Synthesis and Study of Ligands for Pd-Catalyzed C-O and C-N Coupling

by
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B.S. Chemistry
University of California, Berkeley, 2005

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

SCIENCE MASTERS IN ORGANIC CHEMISTRY
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

JULY 2009

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ABSTRACT

A new ligand, AdBrettPhos, was synthesized and its use, along with tBuBrettPhos, in C-O coupling reactions at low temperatures was investigated. Using Pd catalysts containing these ligands, electron-neutral aryl bromides were coupled with phenols at room temperature for the first time. A variety of electron-deficient aryl halides and phenols were also coupled at moderate temperatures in good yields.

In order to probe how the structural features of the ligand affect the catalytic activity of Pd catalysts containing dialkylbiarylphosphines, a series of novel ligands was synthesized and their utility in Pd-catalyzed C-N couplings was investigated. All of these ligands provided competent catalysts for the cross-coupling reactions of aryl halides with primary alkyl or aryl amines. However, in general these catalysts cannot match the rates and low catalyst loadings achieved by BrettPhos-supported Pd-catalysts, with the exception of **L8**, which was shown to be superior to BrettPhos in terms of rate and yield for the coupling of methylamine. The high selectivity for monoarylation of primary amines exhibited by these catalysts indicates that the methoxy substituent *ortho* to phosphorous plays an important role in regulating this selectivity.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

Acknowledgements

I would like to thank my advisor, Steve Buchwald, for all his guidance, support, and understanding. It has been a great privilege to work with him. I would like to thank all of my coworkers in the Buchwald lab, not only are they excellent scientists, they are also a fun group of people to work with. In particular I would like to thank Brett Fors, Dr. Pat Bazinet, Dr. Alex Taylor, Dr. Chong Han, Dr. Tom Kinzel, Dr. Alan Hyde, John Naber, Dr. Jackie Hicks, Dr. Mark Biscoe, and Dr. Don Watson for many helpful discussions; I have learned a great deal from them. Special thanks are due to Brett for teaching me many lab techniques, including how to run calorimetry experiments, and for answering my millions of questions with patience, encouragement and optimism. Special thanks are also due to Pat, whose friendship made life in the lab a lot more fun, for all his advice and support, and for editing this work. I would also like to thank Andrew Musacchio, a promising undergraduate in the group, for testing one of my new ligands.

I would like to acknowledge the people who first introduced me to chemistry research and encouraged me to pursue graduate studies: Prof. Andrew Streitwieser, Prof. Dean Toste, and Dr. David Gorin.

This work is dedicated to my family.

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Chapter 1. Pd-Catalyzed C-O Coupling: Synthesis of Diaryl Ethers

1.1 Introduction

A wide array of biologically active natural products and small molecules contain diaryl ether groups.[1] The transition metal catalyzed coupling of phenols and aryl halides is an attractive means of generating this structural unit, but the existing methods for this transformation are only effective with activated substrates or under harsh conditions, which renders them unsuitable for the synthesis of sensitive compounds such as those with epimerizable stereocenters. This project seeks to develop a catalyst system capable of effecting C-O cross-coupling reactions at room temperature with a wide variety of substrates.

Both copper and palladium catalysts have been shown to catalyze the coupling of phenols and aryl halides, but all reported systems require high reaction temperatures (typically 100-120°C for intermolecular reactions).[2] Additionally, poor results were obtained when either unactivated aryl halides, hetero-aryl halides, or electron-poor phenols were used.[2] Palladium catalysts supported by electron-rich, bulky phosphine ligands have allowed for progress in this area[3-5] and served as the starting point for the current study.

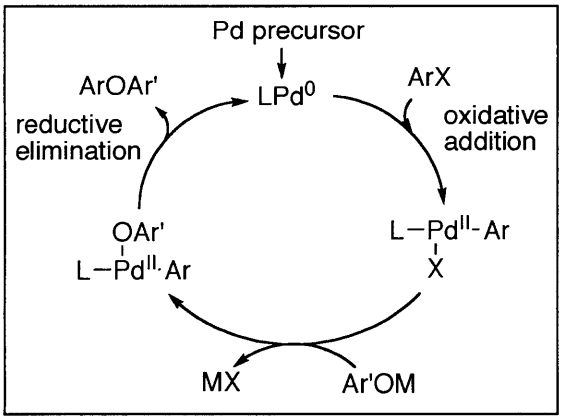


Figure 1. Proposed Catalytic Cycle for C-O Coupling Reactions.

The proposed catalytic cycle for Pd-catalyzed C-O coupling reactions is similar to that proposed for other Pd-catalyzed C-C and C-heteroatom bond forming reactions (Figure 1).[6] Oxidative addition of an aryl halide by a LPd(0) complex provides the $LPd^{II}(Ar)(X)$ complex, which undergoes transmetalation with a metal phenolate to afford the $LPd^{II}(Ar)(OAr')$ complex. Subsequently, reductive elimination of the diaryl ether product from this complex regenerates the active LPd(0) species.

The oxidative addition step is expected to be relatively facile, as Pd/dialkylbiarylphosphine catalyst systems similar to those used for C-O bond forming have been used effectively for C-C and C-N coupling reactions at room temperature[7], and oxidative addition of chlorobenzene has been observed in stoichiometric experiements[8] at -40°C. The transmetalation step has also been shown to occur at room temperature in stoichiometric experiments with Pd^{II} complexes containing electron-rich, bulky phosphine ligands.[9,10] The product forming step, reductive elimination to form a C-O bond is more difficult compared to formation of a C-N bond[11,12]; this is believed to be due to the large energy gap between the Pd-O HOMO and the Pd-C LUMO.[13] Stoichiometric studies of C-heteroatom reductive elimination from Pd complexes have shown that decreasing electron density on the Pd-bound aryl group and increasing electron density on the heteroatom leads to increased reaction rates.[11,12,14,15] Phenoxide ligands are less electron-donating than other heteroatom ligands, such as amides, thiolates, or even alkoxides, and consequently the formation of diaryl ethers has been found to be particularly difficult.[6,14,16] Clearly, ligands which can facilitate C-O reductive elimination from Pd complexes will be needed in order to perform C-O couplings at lower temperatures. In an effort to determine which ligand properties can accelerate

reductive elimination from Pd to form C-O bonds, stoichiometric reactions were studied. Reducing the electron density of the ligand has been found to facilitate reductive elimination,[11,14] however, increasing the steric bulk of the ligand was found to have the greatest accelerating effect on the rate of reductive elimination.[6,10,12,16]

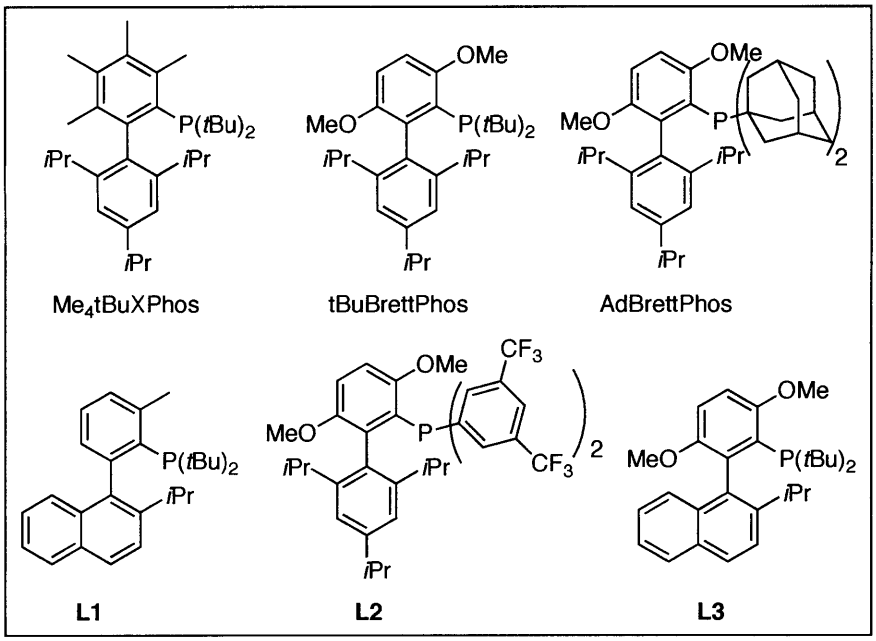


Figure 2. Ligands evaluated in C-O Coupling Reactions

Use of the bulky, electron-rich ligand, Me_4tBuXPhos (Figure 2), in the Pd-catalyzed coupling of previously unreactive electron-neutral aryl chlorides and bromides with phenols has thus far led to the best results.[3] Consequently, we hypothesized that the use of tBuBrettPhos would also lead to an effective catalyst for this reaction because the placement of the methoxy groups is expected to increase electron density, provide conformational rigidity to the catalyst, and therefore promote reductive elimination.[3,17] Substituents at the 2 and 5 positions of the aryl ring on phosphorous greatly increase the barrier to rotation around the P-Ar bond, forcing the Pd to remain over the non-phosphorous-containing aryl ring (Figure 3).[17] This conformation promotes reductive

elimination by forcing the Pd to remain in a sterically crowded environment and holding the aryl ring in position to act as a ligand to the Pd center.

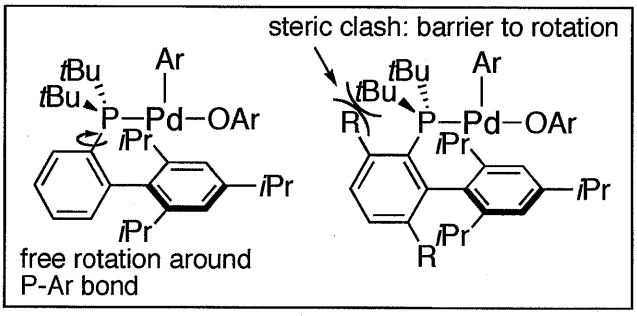


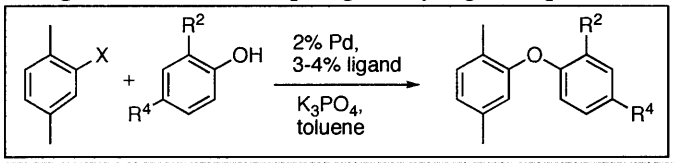
Figure 3. Effect of Substituent *Ortho* to Phosphorous

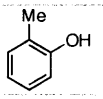
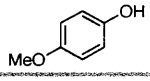
1.2 Results and Discussion

In our initial studies we were pleased to find that palladium acetate with tBuBrettPhos catalyzed the coupling of 2-chloro-1,4-dimethylbenzene with phenol at 100°C in 80% yield in only 2 hours, whereas the same reaction with Me_4tBuXPhos was not complete after 16 h (Table 1, Entries 1-2). Our first attempts at running the reaction at lower temperatures were unsuccessful and suggested that reduction of palladium acetate to an active palladium(0) species is difficult under these conditions. Pre-activation of the Pd catalyst via water activation[18] or phenyl boronic acid activation[19] did not provide any catalytic activity in reactions performed below 100°C. However, use of palladium(0) precursors such as Pd_2dba_3, enabled aryl bromides to be coupled efficiently at 60°C (Entries 5-6). Below this temperature only minimal reactivity was observed, likely due to competitive binding to the Pd atom between dba and the phosphine ligand.[20] In order to avoid competing ligands, more easily activated palladium(II) sources, such as $[Pd(cinnamyl)Cl]_2$, were used and cross-coupling was observed at lower temperatures (40-25°C) with electron-neutral substrates for the first time.

The reaction conditions for the coupling of a model substrate (Entry 7) using tBuBrettPhos as a ligand were optimized and the best results were obtained when using 1% $[Pd(cinnamyl)Cl]_2$, 4% ligand, 1.2 equiv phenol, 2 equiv K_3PO_4, 0.5M in toluene. Aryl bromides react faster than aryl chlorides (Entries 7-8), while aryl iodides are unreactive under these conditions.

Table 1. Comparison of Ligands in C-O Coupling: Varying Temperature and Pd Source

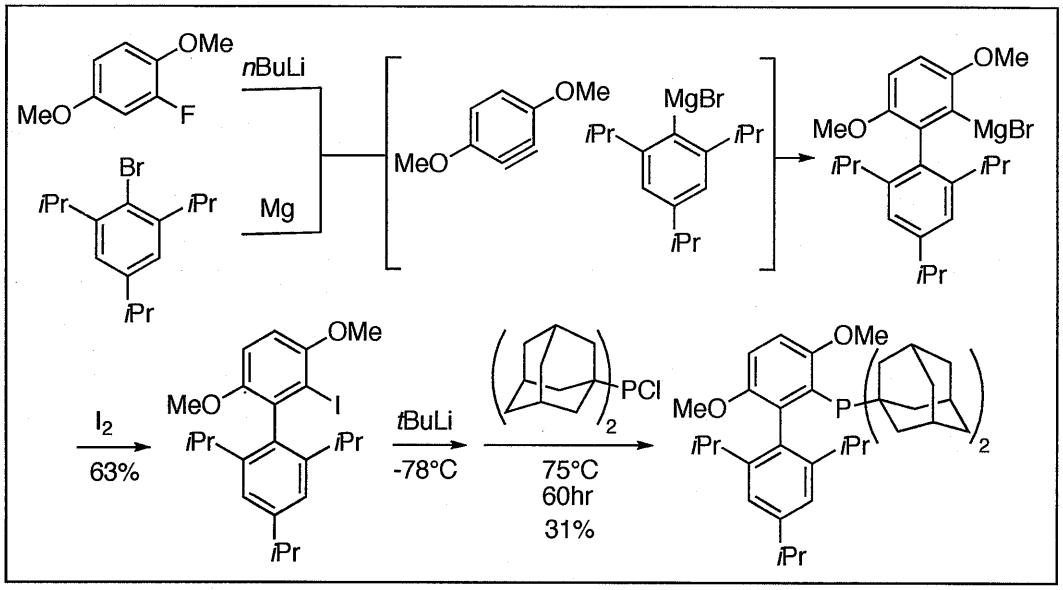


Entry	Temp (°C)	Pd Source	phenol	ArX	Ligand	Time (h)	GC yield (%)
1	100	$Pd(OAc)_2$		Cl	Me_4tBuXPhos	16	64
2	100	$Pd(OAc)_2$		Cl	tBuBrettPhos	2	80
3	100	$Pd(OAc)_2$		Cl	AdBrettPhos	2	85
4	100	$Pd(OAc)_2$		Cl	**L2**	16	84
5	60	Pd_2dba_3		Br	tBuBrettPhos	24	89
6	60	Pd_2dba_3		Br	AdBrettPhos	20	86
7	60	$[Pd(cinnamyl)Cl]_2$		Cl	tBuBrettPhos	24	95
8	60	$[Pd(cinnamyl)Cl]_2$		Br	tBuBrettPhos	4	97
9	60	$[Pd(cinnamyl)Cl]_2$		Br	**L3**	24	89
10	40	$[Pd(cinnamyl)Cl]_2$		Br	tBuBrettPhos	24	87
11	25	$[Pd(allyl)Cl]_2$		Br	tBuBrettPhos	48	45 (1 M)
12	25	$[Pd(cinnamyl)Cl]_2$		Br	tBuBrettPhos	48	50(0.5M) 60 (1 M)
13	25	$[Pd(cinnamyl)Cl]_2$		Br	AdBrettPhos	24	78
14	25	$[Pd(cinnamyl)Cl]_2$		Br	**L3**	48	18
15	25	$[Pd(cinnamyl)Cl]_2$		Br	tBuBrettPhos	48	69
16	25	$[Pd(cinnamyl)Cl]_2$		Br	AdBrettPhos	24	69
17	25	$[Pd(cinnamyl)Cl]_2$		Br	tBuBrettPhos	48	91
18	25	$[Pd(cinnamyl)Cl]_2$		Br	AdBrettPhos	24	96

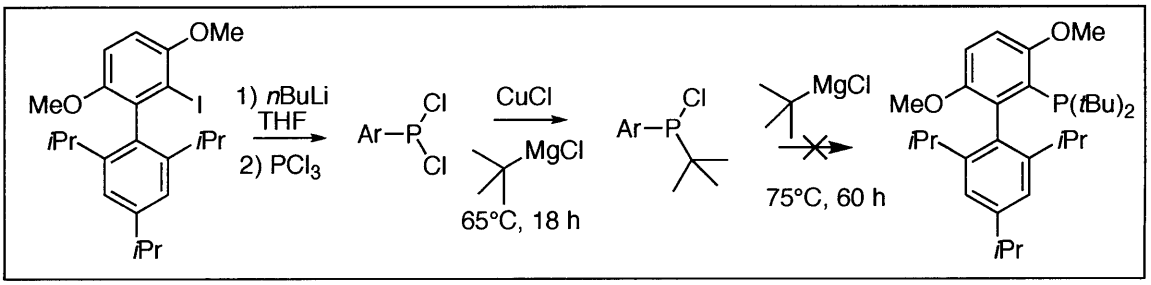
Reaction Conditions: ArX (0.5 mmol), phenol (0.6 mmol), K_3PO_4 (1 mmol), Pd source (2 mol% Pd), ligand (3-4 mol%), toluene (2 mL/mmol); GC yield based on dodecane internal standard.

We hypothesized that an even more sterically demanding ligand would increase the rate of reductive elimination of diaryl ethers from Pd, and thus allow the reaction to proceed more efficiently at lower temperatures. Substituting the *t*Bu groups on the phosphorous atom of BrettPhos with the sterically more demanding adamantyl group

would provide an extremely bulky ligand, AdBrettPhos (Figure 2). The synthesis of AdBrettPhos required the preparation of diadamantylchlorophosphine from adamantane.[21,22] The biaryl moiety of the BrettPhos ligands is synthesized via addition of a Grignard reagent to a benzyne, which is generated in-situ by ortho-lithiation of an aryl fluoride, followed by LiF elimination (Scheme 1).[23] Adding the biaryl lithium to a dialkylchlorophosphine provides the biarylphosphine in good yields when the alkyl groups on phosphorous are cyclohexyl groups or smaller. However, chloride substitution for the more sterically hindered di-*tert*-butyl-, or di(1-adamantyl)- chlorophosphines is difficult: it requires prolonged heating in a sealed tube and provides only modest yields of the desired ligands. In an effort to develop a more efficient route to diadamantyl and di-*tert*-butyl biarylphosphine ligands, and eliminate the need to prepare Ad_2PCl, I attempted the route shown in Scheme 2. Unfortunately, even under prolonged heating the mono-addition product predominated. Perhaps this route could be further explored as a method for preparing biarylphosphines with two different alkyl substituents, in order to generate P-chiral ligands.

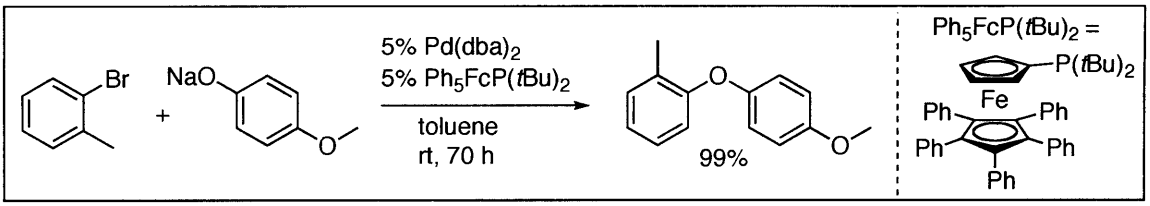


Scheme 1. Synthesis of AdBrettPhos



Scheme 2. Attempted alternate route to tBuBrettPhos

The only reported example of a palladium-catalyzed intermolecular C-O coupling to form a diaryl ether at room temperature is the reaction of the preformed sodium phenolate salt of electron-rich 4-methoxyphenol with 2-bromotoluene which requires 5% Pd and takes 70 h (Scheme 3).[4] Using AdBrettPhos/$[Pd(cinnamyl)Cl]_2$ and 4-methoxyphenol (instead of the sodium salt) yielded a similar ether product in 24 h with only 2% Pd in 96% yield (Entry 16). Even more challenging substrates, such as phenol, which lacks an electron-donating substituent to enhance the nucleophilicity, can be coupled at room temperature in good yield with AdBrettPhos (Entry 11).

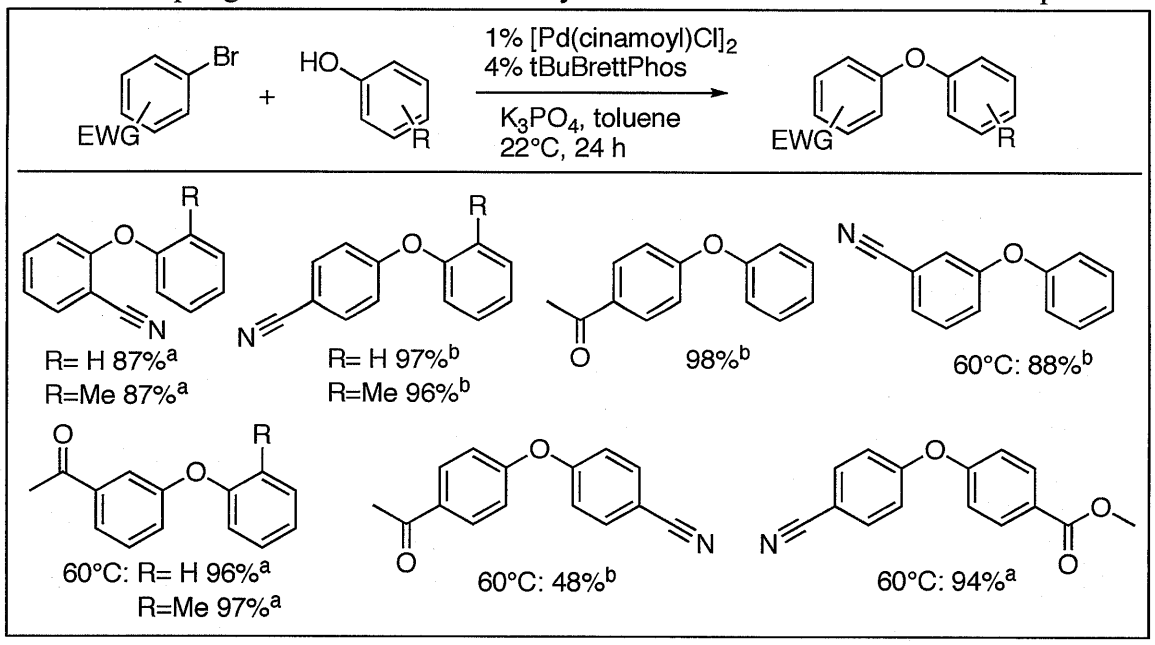


Scheme 3. Only Reported Example of Pd-catalyzed Diaryl Ether Formation at Room Temp.[4]

Another way to promote reductive elimination besides increased steric bulk would be to make the Pd center more electron-deficient.[14] To investigate this approach, I tested **L2** (Figure 2). Reactions performed at 100°C (Entry 4) worked well, however, when the reactions were run at lower temperatures or with difficult substrates (3-bromoanisole for example) no product was formed. Attempts to synthesize a dialkylbiarylphosphine ligand with electron withdrawing groups on the biaryl moiety and bulky alkyl substituents on phosphorous (such as adamantyl or *t*Bu) were thus far unsuccessful.

Despite the successful use of tBu and AdBrettPhos as ligands for the Pd-catalyzed coupling of electron-neutral aryl bromides with phenols at room temperature, difficult substrates such as heteroaryl halides and electron deficient phenols are not coupled very efficiently, even at elevated temperatures. Based on the successful use of **L1** (Figure 2) in coupling reactions of difficult substrates[3], I hypothesized that a hybrid between **L1** and tBuBrettPhos would be a good ligand for C-O coupling, therefore I synthesized **L3**. Comparison studies showed that C-O coupling reactions performed with **L3** provide the diaryl ether product, but in lower yields than when tBuBrettPhos is used (Entries 9, 12). Coupling reactions of alkyl alcohols performed with **L3** also provide ether products, but in lower yields than reactions performed with previously reported catalyst systems.[24]

Table 2. Coupling of Electron Deficient Aryl Halides and Phenols at Room Temperature

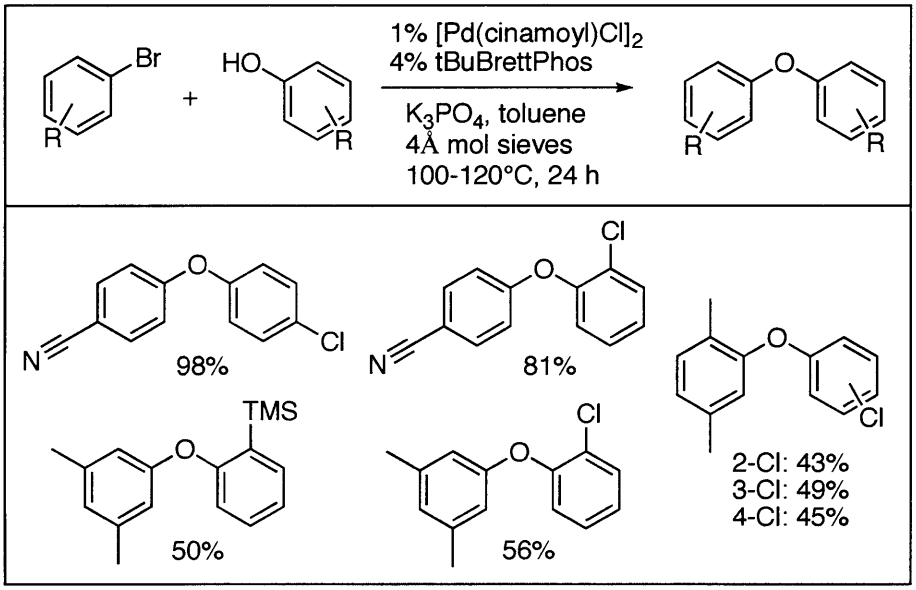


[a] Corrected GC yield based on dodecane internal standard. [b] Isolated yield.

Aryl halides bearing electron-withdrawing groups are more facile substrates for palladium catalyzed C-O coupling,[6] and many can be coupled at room temperature in good yields using tBuBrettPhos (Table 2). However, reactions involving less activated

substrates, such as aryl halides with electron-withdrawing groups in the 3-position, require moderate heating to reach complete conversion. Coupling reactions of activated aryl halides with electron-deficient phenols, which are particularly difficult substrates, can also be performed at moderate temperatures (Table 2).

Table 3. Coupling of Phenols Bearing Reactive Functional Groups



Substrates bearing ortho-substituents promote reductive elimination by increasing the steric crowding around the Pd center. We hoped to take advantage of this property by coupling phenols containing an ortho-substituent that could serve as a handle for further chemical modifications. Phenols bearing ortho-TMS, Cl, Br, and I groups were investigated. The iodo and bromo phenols were unreactive, but the TMS and chloro-substituted phenols were coupled in moderate to good yields (Table 3). In general, trace adventitious water in C-O cross-coupling reactions has a negative effect on the yield due to conversion of some of the aryl halide to phenol,[25] and subsequent coupling of that phenol to form a symmetrical diaryl ether biproduct.[24] This side reaction is particularly problematic when reactions using difficult substrates are performed because the rates of

C-O coupling to form the desired ether products are much slower. Therefore reaction conditions were further optimized to eliminate as much water as possible. The best results were obtained when K_3PO_4 and 4Å molecular sieves were flame-dried prior to addition of the other reagents.

1.3 Conclusions

A new dialkylbiarylphosphine ligand, AdBrettPhos, was synthesized and its use, along with tBuBrettPhos, in Pd-catalyzed C-O coupling reactions was investigated. Using Pd catalysts containing these ligands, coupling reactions of electron-neutral aryl bromides with phenols to form diaryl ethers were performed at room temperature for the first time. Additionally, a variety of electron-deficient aryl halides and phenols were also coupled at moderate temperatures in good yields. In general, this new type of biarylphosphine ligand has proven to be very effective, which suggests that its use might enable the C-O cross-coupling of a wide variety of substrates at low temperatures.

1.4 Experimental Section

General Reagent Information

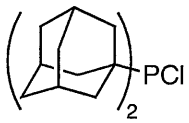
All reactions were carried out under an argon atmosphere in oven-dried re-sealable screw top test tubes or Schlenk tubes. $Pd(OAc)_2$ was a gift from BASF. Pd_2dba_3 and $[Pd(allyl)Cl]_2$ were purchased from Aldrich and $[Pd(cinnamyl)Cl]_2$ was synthesized via literature procedure[26]. Aryl halides and phenols were obtained from commercial sources (Aldrich, Alfa Aesar, Avocado, Acros, TCI America) and used without further purification. The 1,4-dimethoxyfluorobenzene was purchased from Synquest Labs, Inc. and used as received. Potassium phosphate (Riedel-de-Haën) was stored in bulk in an N_2-filled glovebox. Small portions were taken outside the box in glass vials and weighed in the air. Toluene was obtained from J. T. Baker in CYCLE-TAINER kegs which were purged with argon for two hours and subsequently passed through two columns of neutral alumina and copper(II) oxide under a pressure of argon for further purification. Ligands **L1**[3], **L2**[27], and tBuBrettPhos[28] and ligand precursors 2-iodo-2',4',6'-triisopropyl-3,6-dimethoxybiphenyl[23] and 1-bromo-2-isopropylnaphthalene[17] were synthesized using literature procedures. Silica column chromatography was performed using a Biotage SP4 Flash Purification System on KP-Sil silica cartridges.

General Analytical Information

Compounds were characterized by ^1H NMR, ^{13}C NMR, melting point, IR spectroscopy and, in certain cases, elemental analysis or high resolution mass spectrometry. (Copies of ^1H-NMR and ^{13}C NMR spectra are provided in Appendix A for all new compounds). Data of known compounds were compared with existing literature characterization data and the references are given. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument. The chemical shifts are reported in parts per million (ppm) based on the reference of the deuterated solvent. IR spectra were measured using a Perkin – Elmer 2000 FTIR. All GC analyses were performed on a Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). GC yields and conversions were reported as referenced to dodecane as an internal standard. GC-MS analyses were performed on an Agilent 6850 instrument with an Agilent 5975 inert Mass Selective Detector. Melting points were measured using a Mel-

Temp II capillary apparatus. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

Ligand Syntheses

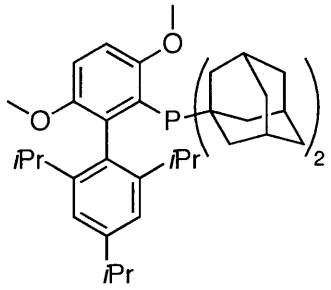


Di(1-adamantyl)chlorophosphine[21,22] An oven-dried 500 mL Schlenk flask, which was cooled under argon, was equipped with a magnetic stir bar, charged with adamantane (25 g, 0.18 mol) and aluminum trichloride (26 g, 0.19 mol), fitted with a reflux condenser, and purged with argon. Phosphorous trichloride (75 mL, 0.86 mol) was added and the reaction mixture was heated at reflux for 5 h. The reaction vessel was then cooled to room temperature, and the condenser was replaced with a distillation head. The phosphorous trichloride was removed by distillation, and the remaining orange residue was cooled in an ice bath and dissolved in chloroform (250 mL). Water (250 mL) was added slowly to the cooled solution, and the resulting mixture was allowed to stir at room temperature overnight. The organic phase was separated and washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure to yield di(1-adamantyl)phosphinyl chloride[21] as an off-white solid (40 g, 99%), which was used directly without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.18-2.12 (m, 6H), 2.09-2.02 (m, 3H), 1.79-1.71 (m, 6H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 86.62 ppm.

An oven-dried 100 mL Schlenk flask, which was cooled under argon, was equipped with a magnetic stir bar, charged with diadamantylphosphinylchloride (2 g, 5.67 mmol), fitted with a septum and purged with argon. THF (25 mL) was added and the resulting suspension was cooled to -10°C. Lithium aluminum hydride (95% powder, 516 mg, 13.6 mmol) was added in 3 portions. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction vessel was cooled to -10°C and the unreacted $LiAlH_4$ was quenched by dropwise addition of 1 M HCl (12 mL). The reaction mixture was then allowed to warm to room temperature and diethyl ether (20 mL) was added via syringe. The stirring was stopped to allow the solids to settle and the organic layer was transferred via cannula to a separate Schlenk flask containing magnesium sulfate. The dried organic layer was then separated from the

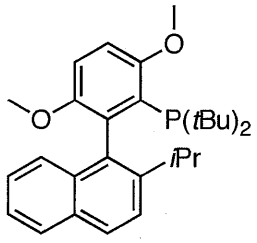
drying agent by transfer through a filter cannula, the solvent was removed *in vacuo* to yield the di(1-adamantyl)phosphine[21] as white solid, which was used directly without purification. ^{1}H NMR (400 MHz, C_6D_6) δ: 2.04-1.89 (m, 6H), 1.88-1.82 (m, 3H), 1.67-1.62 (m, 6H) ppm. ^{31}P NMR (162 MHz, C_6D_6) δ: 18.62 ppm.

To the Schlenk flask containing diadamantylphosphine under argon was added carbon tetrachloride (10 mL), and the resulting solution was heated to 50°C for 16 h. The solvent was removed *in vacuo* to yield the title compound as a white solid (1.35 g, 70% over 2 steps). ^{1}H NMR (400 MHz, C_6D_6) δ: 2.05-1.94 (m, 6H), 1.86-1.78 (m, 3H), 1.61-1.52 (m, 6H) ppm. ^{31}P NMR (162 MHz, C_6D_6) δ: 140.39 ppm.



2-Diadamantylphosphino-2',4',6'-triisopropyl-3-methoxybiphenyl An oven-dried 50 mL Schlenk tube was equipped with a magnetic stir bar, charged with 2-iodo-2',4',6'-triisopropyl-3,6-dimethoxybiphenyl (750 mg, 1.6 mmol), fitted with a septum, and purged with argon. THF (8 mL) was added and the solution was cooled to -78°C. *t*BuLi (1.7 M in pentane, 1.94 mL, 3.3 mmol) was added dropwise via syringe and the reaction mixture was allowed to stir for 10 minutes. CuCl (160 mg, 1.6 mmol) was added quickly in one portion by removing the septum. The cold bath was removed and the reaction mixture was allowed to warm to room temperature, followed by addition of a solution of di(1-adamantyl)chlorophosphine (540 mg, 1.6 mmol) in THF (4 mL) via cannula. The reaction vessel was sealed with a teflon screw-cap and heated at 75°C for 60 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed four times with 30% aqueous ammonium hydroxide. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow oily residue was dissolved in a mixture of dichloromethane and ethyl acetate whereupon a white precipitate formed. The precipitate was collected by vacuum filtration to yield the title compound (as a 1:1 crystal w/DCM; DCM could be

removed by dissolving crystals in benzene and concentrating under reduced pressure) as a white powder (303 mg, 35% yield), mp 232-234°C. ^{1}H NMR (400 MHz, C_6D_6) δ: 7.26 (s, 2H), 6.53 (d, J = 8.9, 1H), 6.49 (d, J = 8.9, 1H), 3.39 (s, 3H), 3.08 (s, 3H), 2.92 (septet, J = 7.0, 2H), 2.87 (septet, J = 7.0, 1H), 2.20 – 2.06 (m, 12H), 1.97-1.92 (m, 6H), 1.80 – 1.64 (m, 12H), 1.55 (d, J = 6.7, 6H), 1.27 – 1.16 (m, 12H) ppm. ^{13}C NMR (101 MHz, C_6D_6) δ: 156.37, 153.23, 153.11, 148.20, 147.57, 141.50, 141.11, 134.22, 134.15, 126.45, 125.98, 120.95, 111.53, 108.83, 53.71, 42.96, 42.82, 39.77, 39.47, 37.84, 34.83, 31.98, 30.17, 30.08, 26.48, 24.61, 24.50 ppm. (Observed complexity is due to P-C splitting). ^{31}P NMR (161 MHz, C_6D_6) δ: 36.25 ppm. IR (neat, cm^{-1}): 2902, 1653, 1559, 1457, 1419, 1251. Anal. Calcd. for $C_{44}H_{63}Cl_2O_2P$: C, 72.81; H, 8.75. Found: C, 72.57; H, 8.73.



Di-*tert*-butyl(2-(2-isopropylnaphthalen-1-yl)-3,6-dimethoxyphenyl)phosphine (L3) An oven-dried three-neck 100 mL round bottom flask was equipped with a magnetic stir, fitted with a reflux condenser, glass stopper and rubber septum, and charged with magnesium shavings (348 mg, 14.5 mmol). The flask was purged with argon and then THF (35 mL), 1-bromo-2-isopropylnaphthalene (3 g, 12 mmol), and 1,2-dibromoethane (30 μL) were added via syringe. The reaction mixture was heated at reflux for 1 h, and then allowed to cool to room temperature. A separate oven-dried 200 mL Schlenk flask, which was equipped with a magnetic stir bar and fitted with a septum, was purged with argon and then THF (60 mL) and 1,4-dimethoxy-2-fluorobenzene (936 mg, 6 mmol) were added via syringe. The reaction vessel was cooled in a -78°C bath and n-BuLi (2.5 M in hexane, 2.4 mL, 6 mmol) was added dropwise via syringe. The solution was stirred for 30 min. followed by addition of the Grignard reagent (prepared in the first reaction vessel) via cannula over a 20 min. period. After the addition was complete, the cold bath was removed and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0°C and a solution of iodine in THF (2 M, 24 mL, 12 mmol) was added via cannula over 15 min. The mixture was allowed to warm to room

temperature and stirred for 1 h. The excess I_2 was quenched by addition of saturated aq. $Na_2S_2O_3$ until the dark red color disappeared. The reaction mixture was extracted twice with diethyl ether, and the combined organic layers were washed with brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified via silica column eluting with a gradient of 0-25% EtOAc/hexanes to provide the biaryl iodide as a pale yellow solid (970 mg, 37%), which was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, J=8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.39 (ddd, J=8.0, 6.8, 1.2 Hz, 1H), 7.30 (ddd, J=8.0, 6.8, 1.2 Hz, 1H), 7.16 (d, J=8.0 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H), 6.91 (d, J=8.0 Hz, 1H), 3.94 (s, 3H), 3.58 (s, 3H), 2.67 (septet, J= 6.8, 1H), 1.27 (d, J=6.8, 3H), 1.13 (d, J=6.8, 3H) ppm.

An oven-dried 50 mL Schlenk tube was equipped with a magnetic stir bar, charged with the biaryl iodide (400 mg, 0.93 mmol), fitted with a septum, and purged with argon. THF (5 mL) was added and the solution was cooled to -78°C. *t*BuLi (1.7 M in pentane, 1.12 mL, 1.9 mmol) was added dropwise via syringe and the reaction mixture was allowed to stir for 10 minutes. CuCl (92 mg, 0.93 mmol) was added quickly in one portion by removing the septum. The cold bath was removed and the reaction mixture was allowed to warm to room temperature, followed by addition of di-*tert*-butylchlorophosphine (168 mg, 0.93 mmol) via syringe. The reaction vessel was sealed with a teflon screw-cap and heated at 75°C for 60 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed four times with 30% aqueous ammonium hydroxide. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystallized from methanol to yield the title compound as white crystals (46 mg, 11%), mp 85-87°C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 7.83 (d, J = 8.6, 1H), 7.75 (d, J = 8.0, 1H), 7.51 (d, J = 8.6, 1H), 7.29 (ddd, J = 8.1, 6.5, 1.4, 1H), 7.17 – 7.12 (m, 1H), 7.09 (d, J = 7.9, 1H), 7.06 (d, J = 9.0, 1H), 6.98 (d, J = 9.0, 1H), 3.81 (s, 3H), 3.51 (s, 3H), 2.91 (septet, J = 6.9, 1H), 1.37 (d, J = 6.8, 3H), 1.19 (d, J = 12.3, 9H), 0.96 (d, J = 6.8, 3H), 0.77 (d, J = 12.0, 9H).. ^{13}C NMR (101 MHz, CD_2Cl_2) δ: 156.65, 156.63, 152.91, 152.80, 143.88, 143.85, 138.81, 138.42, 134.60, 134.51, 133.71, 132.23, 128.60, 127.91, 127.83, 127.39, 124.83, 124.71, 123.80, 112.82, 109.76, 56.06, 54.43, 34.30, 34.04, 33.40, 33.12, 32.12, 31.95, 31.86,

31.70, 31.49, 31.47, 24.76, 22.81 ppm. (Observed complexity is due to P-C splitting). ^{31}P NMR (161 MHz, C_6D_6) δ: 32.92 ppm. IR (neat, cm^{-1}): 2958, 1457, 1426, 1253, 1073, 817. Anal. Calcd. for $C_{29}H_{39}O_2P$: C, 77.30; H, 8.72. Found: C, 77.02; H, 8.64.

General Procedure for Examples Described in Table 1

An oven-dried screw-top tube with a teflon septum was cooled to room temperature under argon pressure. The tube was charged with K_3PO_4 (1 mmol) and the phenol (0.6 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times). Then aryl halide (0.5 mmol) and a toluene solution (1 mL) containing the ligand (4 mol%) and the Pd complex (2 mol% Pd) were added via syringe through the septum. (The ligand/Pd solution was prepared in an oven-dried screw-top volumetric flask with a teflon septum. After addition of the ligand/Pd, the flask was evacuated and backfilled with argon, this procedure was repeated three times, followed by addition of toluene.) The reaction mixture was then allowed to stir at the specified temperature. After the specified time, the mixture was cooled to room temperature and dodecane was added as an internal standard. The reaction mixture was diluted with ethyl acetate, washed with water, and analyzed by GC.

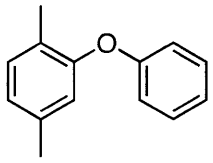
General Procedure for Examples Described in Table 2

An oven-dried screw-top tube with a teflon septum was cooled to room temperature under argon pressure. The tube was charged with K_3PO_4 (1 mmol) and the phenol (0.6 mmol). (Aryl halides which are solids at room temperature were also added at this time.) The vessel was evacuated and backfilled with argon (this process was repeated a total of three times). Then the aryl halide (0.5 mmol) and a toluene solution (1 mL) containing tBuBrettPhos (4 mol%) and $[Pd(cinnamyl)Cl]_2$ (1 mol%) were added via syringe through the septum. (The ligand/Pd solution was prepared in an oven-dried screw-top volumetric flask with a teflon septum. After addition of the ligand/Pd, the flask was evacuated and backfilled with argon, this procedure was repeated three times, followed by addition of toluene.) The reaction mixture was then allowed to stir at the specified temperature (either 25 or 60°C) for 24 h. At this time dodecane internal standard was added and the mixture was diluted with ethyl acetate, washed with water, analyzed by GC, and

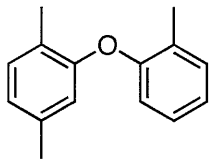
concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

General Procedure for Examples Described in Table 3

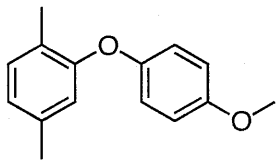
A screw-top tube with a teflon septum was charged with K_3PO_4 (1 mmol) and 4Å mol. sieves (50 mg). The tube was then flame dried under active vacuum. (The tube was cooled under argon pressure, followed by the addition of aryl halides and phenols which are solids at room temperature.) The vessel was evacuated and backfilled with argon (this process was repeated a total of three times). Then the phenol (0.6 mmol), aryl halide (0.5 mmol) and a toluene solution (1 mL) containing tBuBrettPhos (4 mol%) and $[Pd(cinnamyl)Cl]_2$ (1 mol%) were added via syringe through the septum. (The ligand/Pd solution was prepared in an oven-dried screw-top volumetric flask with a teflon septum. After addition of the ligand/Pd, the flask was evacuated and backfilled with argon, this procedure was repeated three times, followed by addition of toluene.) The reaction mixture was then heated at 100-120°C for 24 h. At this time dodecane (as an internal standard) was added and the mixture was diluted with ethyl acetate, washed with water, analyzed by GC, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.



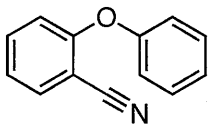
2,5-Dimethyldiphenylether[6] Following the general procedure for Table 1, a mixture of $Pd(OAc)_2$ (2.25 mg, 0.01 mmol), tBuBrettPhos (7 mg, 0.015 mmol), phenol (56 mg, 0.6 mmol), chloro-*p*-xylene (67 μL, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was heated at 100°C for 2 h. The crude product was purified on a silica column eluting with hexanes to yield the title compound as a clear oil (76 mg, 77% isolated yield, 80% GC yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.27 (m, 2H), 7.13 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.91-6.87 (m, 3H), 6.74 (s, 1H), 2.28 (s, 3H), 2.19 (s, 3H) ppm. IR (neat, cm^{-1}): 1578, 1490, 1254, 1217, 1117.



2,2′,5-Trimethyldiphenylether[6] Following the general procedure for Table 1, a mixture of $Pd(OAc)_2$ (2.25 mg, 0.01 mmol), tBuBrettPhos (7 mg, 0.015 mmol), *o*-cresol (65 mg, 0.6 mmol), chloro-*p*-xylene (67 μL, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was heated at 100°C for 2 h. The crude product was purified on a silica column eluting with hexanes to yield the title compound as a clear oil (87 mg, 81% isolated yield, 80% GC yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (dd, J = 7.4, 1.0 Hz, 1H), 7.15 – 7.08 (m, 2H), 7.00 (td, J = 7.4, 1.2 Hz, 1H), 6.83 (d, J = 7.3 Hz, 1H), 6.73 – 6.67 (m, 1H), 6.55 (d, J = 6.8 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H) ppm. IR (neat, cm^{-1}): 1491, 1255,1227, 1185, 1122.

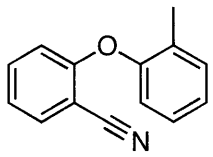


2,5-Dimethyl-4′-methoxydiphenylether[6] Following the general procedure for Table 1, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 4-methoxyphenol (75 mg, 0.6 mmol), bromo-*p*-xylene (69 μL, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was heated at 40°C for 24 h. The crude product was purified on a silica column eluting with a gradient of 0-10% ethyl acetate/hexanes to yield the title compound as a white solid (94 mg, 82% isolated yield, 96% GC yield), mp 56-58°C (lit.[6] mp 55-56°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (dd, J = 16.2, 8.1 Hz, 1H), 6.96 – 6.78 (m, 5H), 6.58 (s, 1H), 3.84 – 3.77 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H) ppm. IR (neat, cm^{-1}): 1502, 1242, 1210, 1116, 1038.

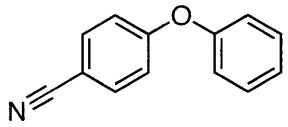


2-Phenoxybenzonitrile[29] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), phenol (56 mg, 0.6 mmol), 2-bromobenzonitrile (91 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was allowed to stir at room temperature for 24 h. A portion of the crude

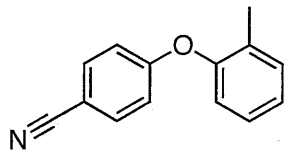
product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a yellow oil (87% GC yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, J = 7.5, 1.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.44 – 7.37 (m, 2H), 7.25 – 7.19 (m, 1H), 7.14 (dd, J = 7.5, 1.0 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.86 (d, J = 8.5 Hz, 1H) ppm. IR (neat, cm^{-1}): 2231, 1485, 1449, 1249, 757.



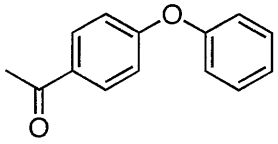
2-Cyano-2′-methyldiphenylether[3] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), *o*-cresol (65 mg, 0.6 mmol), 2-bromobenzonitrile (91 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was allowed to stir at room temperature for 24 h. A portion of the crude product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a yellow oil (87% GC yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, J = 7.7, 1.7 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.32 – 7.27 (m, 1H), 7.23 (td, J = 7.7, 1.9 Hz, 1H), 7.17 (td, J = 7.4, 1.4 Hz, 1H), 7.08 (td, J = 7.5, 0.8 Hz, 1H), 6.99 (dd, J = 7.9, 1.1 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 2.22 (s, 3H) ppm. IR (neat, cm^{-1}): 2229, 1484, 1448, 1251, 756.



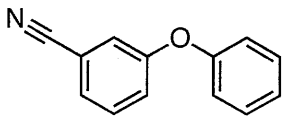
4-Cyanodiphenylether[3] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), phenol (56 mg, 0.6 mmol), 4-bromobenzonitrile (91 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was allowed to stir at room temperature for 24 h. The crude product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a yellow oil (95 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 – 7.57 (m, 2H), 7.46 – 7.37 (m, 2H), 7.26 – 7.21 (m, 1H), 7.10 – 7.04 (m, 2H), 7.04 – 6.97 (m, 2H) ppm. IR (neat, cm^{-1}): 2227, 1588, 1485, 1247, 1167.



4-(2′-methylphenoxy)benzonitrile[30] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), *o*-cresol (65 mg, 0.6 mmol), 4-bromobenzonitrile (91 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was allowed to stir at room temperature for 24 h. The crude product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a clear oil (100 mg, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.61 – 7.55 (m, 2H), 7.32 – 7.21 (m, 2H), 7.17 (td, J = 7.4, 1.3, 1H), 6.98 (dd, J = 7.9, 1.1, 1H), 6.93 – 6.88 (m, 2H), 2.17 (s, 3H) ppm. IR (neat, cm^{-1}): 2226, 1604, 1503, 1248, 1180.

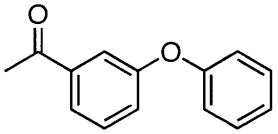


4-Phenoxyacetophenone[31] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), phenol (56 mg, 0.6 mmol), 4-bromoacetophenone (100 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was allowed to stir at room temperature for 24 h. The crude product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a white solid (105 mg, 98%) mp 51-53°C (lit.[31] mp 51°C). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97 – 7.91 (m, 2H), 7.44 – 7.37 (m, 2H), 7.23 – 7.17 (m, 1H), 7.07 (ddd, J = 4.6, 3.4, 1.9 Hz, 2H), 7.03 – 6.97 (m, 2H), 2.58 (s, 3H). IR (neat, cm^{-1}): 1680, 1586, 1490, 1242, 1166.

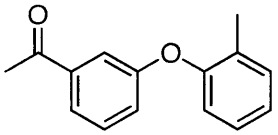


3-Phenoxybenzonitrile[32] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), phenol (56 mg, 0.6 mmol), 3-bromobenzonitrile (91 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was heated at 60°C for 24 h. The crude product was purified on a silica

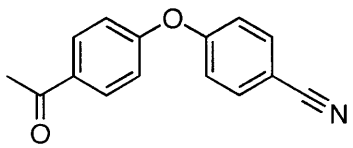
column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a clear oil (86 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 – 7.33 (m, 4H), 7.25 – 7.17 (m, 3H), 7.06 – 7.01 (m, 2H) ppm. IR (neat, cm^{-1}): 2232, 1579, 1481, 1259.



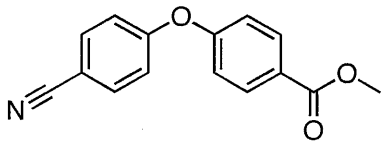
3-Phenoxyacetophenone[33] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), phenol (56 mg, 0.6 mmol), 3-bromoacetophenone (100 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was heated at 60°C for 24 h. A portion of the crude product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a yellow oil (96% GC yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 – 7.66 (m, 1H), 7.60 – 7.56 (m, 1H), 7.43 (t, J = 7.9, 1H), 7.40 – 7.33 (m, 2H), 7.21 (ddd, J = 8.1, 2.5, 0.9, 1H), 7.18 – 7.12 (m, 1H), 7.05 – 6.99 (m, 2H), 2.58 (s, 3H) ppm. IR (neat, cm^{-1}):1687, 1581, 1490, 1437, 1267, 1226.



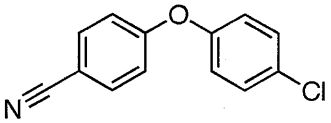
3-(2′-Methylphenoxy)acetophenone[6] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), *o*-cresol (65 mg, 0.6 mmol), 3-bromoacetophenone (100 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was heated at 60°C for 24 h. A portion of the crude product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a yellow oil (97% GC yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, J = 7.7 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.19 (td, J = 7.9, 1.7 Hz, 1H), 7.10 (td, J = 8.4, 2.2 Hz, 2H), 6.93 – 6.89 (m, 1H), 2.57 (s, 3H), 2.24 (s, 3H) ppm. IR (neat, cm^{-1}):1687, 1578, 1482, 1438, 1267, 1233.



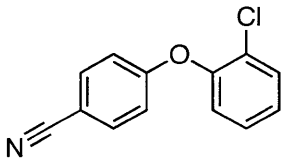
4-(4-Acetyl-phenoxy)-benzonitrile[3] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 4-cyanophenol (71 mg, 0.6 mmol), 4-bromoacetophenone (100 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was heated at 60°C for 24 h. The crude product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a white solid (57 mg, 48%), mp 103-105°C (lit.[3] mp 100-102°C). ^{1}H NMR (400 MHz, $CDCl^3$) δ: 8.04 – 7.99 (m, 2H), 7.69 – 7.64 (m, 2H), 7.13 – 7.06 (m, 4H), 2.60 (s, 3H). IR (neat, cm^{-1}): 2232, 1670, 1593, 1498, 1246.



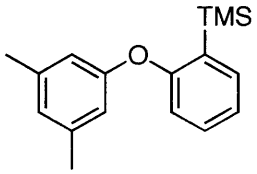
4-(4-Cyano-phenoxy)-benzoic acid methyl ester[3] Following the general procedure for Table 2, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), methyl 4-hydroxybenzoate (152 mg, 0.6 mmol), 4-bromobenzonitrile (91 mg, 0.5 mmol), and K_3PO_4 (212 mg, 1 mmol) in toluene (1 mL) was heated at 60°C for 24 h. A portion of the crude product was purified on a silica column eluting with a gradient of 0-20% ethyl acetate/hexanes to yield the title compound as a white solid (94% GC yield), mp 105-107°C (lit.[3] colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 – 8.03 (m, 2H), 7.70 – 7.61 (m, 2H), 7.10 – 7.05 (m, 4H), 3.92 (s, 3H) ppm. IR (neat, cm^{-1}): 2230, 1713, 1597, 1500, 1284, 1245.



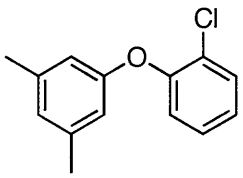
4-(4′-Chlorophenoxy)benzonitrile[3,34] Following the general procedure for Table 3, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 4-chlorophenol (77 mg, 0.6 mmol), 4-bromobenzonitrile (91 mg, 0.5 mmol), K_3PO_4 (212 mg, 1 mmol), and 4Å mol. sieves (50 mg) in toluene (1 mL) was heated at 120°C for 24 h. The crude product was purified on a silica column eluting with a gradient of 0-10% ethyl acetate/hexanes to yield the title compound as a pale yellow solid (114 mg, 98%), mp 85-88°C (lit.[34] mp 81-82°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 – 7.56 (m, 2H), 7.42 – 7.34 (m, 2H), 7.05 – 6.96 (m, 4H) ppm. IR (neat, cm^{-1}): 2226, 1484, 1253, 1083, 823.



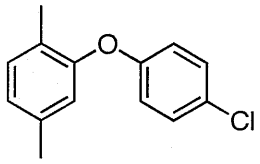
4-(2′-Chlorophenoxy)benzonitrile[34] Following the general procedure for Table 3, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 2-chlorophenol (61 μL, 0.6 mmol), 4-bromobenzonitrile (91 mg, 0.5 mmol), K_3PO_4 (212 mg, 1 mmol), and 4Å mol. sieves (50 mg) in toluene (1 mL) was heated at 120°C for 24 h. The crude product was purified on a silica column eluting with a gradient of 0-10% ethyl acetate/hexanes to yield the title compound as a pale yellow solid (94 mg 81%), mp 74-76°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 – 7.58 (m, 2H), 7.51 (dd, J = 8.0, 1.5 Hz, 1H), 7.33 (td, J = 8.0, 1.6 Hz, 1H), 7.23 (td, J = 7.8, 1.6 Hz, 1H), 7.13 (dd, J = 8.0, 1.5 Hz, 1H), 6.97 – 6.91 (m, 2H) ppm. IR (neat, cm^{-1}): 2227, 1607, 1494, 1248, 1061.



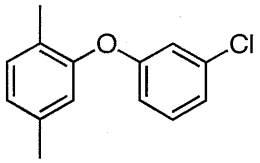
3,5-Dimethyl-2′-(trimethylsilyl)diphenyl ether Following the general procedure for Table 3, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 2-trimethylsilylphenol (100 mg, 0.6 mmol), 5-bromo-*m*-xylene (68 μL, 0.5 mmol), K_3PO_4 (212 mg, 1 mmol), and 4Å mol. sieves (50 mg) in toluene (1 mL) was heated at 120°C for 24 h. The crude product was purified on a silica column eluting with hexanes to yield the title compound as a clear oil (68 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 – 7.46 (m, 1H), 7.30 (ddd, J = 8.3, 7.4, 1.8, 1H), 7.09 (td, J = 7.3, 0.9, 1H), 6.80 (d, J = 8.2, 1H), 6.74 (s, 1H), 6.62 (s, 2H), 2.29 (s, 6H), 0.30 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.40, 157.43, 139.71, 135.43, 130.80, 130.56, 124.99, 122.81, 117.37, 116.82, 77.55, 77.23, 76.91, 21.54, -0.71 ppm. IR (neat, cm^{-1}): 1466, 1435, 1300, 1208, 839.



2-Chloro-3′,5′-dimethyldiphenylether[35] Following the general procedure for Table 3, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 2-chlorophenol (61 μL, 0.6 mmol), 5-bromo-*m*-xylene (68 μL, 0.5 mmol), K_3PO_4 (212 mg, 1 mmol), and 4Å mol. sieves (50 mg) in toluene (1 mL) was heated at 120°C for 24 h. The crude product was purified on a silica column eluting with hexanes to yield the title compound as a clear oil (65 mg, 56%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.45 (dd, J = 8.0, 1.6, 1H), 7.21 (td, J = 7.8, 1.6, 1H), 7.07 (td, J = 7.7, 1.5, 1H), 6.98 (dd, J = 8.1, 1.5, 1H), 6.75 (s, 1H), 6.59 (s, 2H), 2.28 (s, 6H) ppm. IR (neat, cm^{-1}): 1580, 1476, 1232, 1138, 1060.

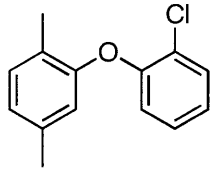


4-Chloro-2′,5′-dimethyldiphenylether Following the general procedure for Table 3, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 4-chlorophenol (77 mg, 0.6 mmol), bromo-*p*-xylene (69 μL, 0.5 mmol), K_3PO_4 (212 mg, 1 mmol), and 4Å mol. sieves (50 mg) in toluene (1 mL) was heated at 120°C for 24 h. The crude product was purified on a silica column eluting with hexanes to yield the title compound as a clear oil (52 mg, 45%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29 – 7.22 (m, 2H), 7.14 (d, J = 7.6, 1H), 6.92 (d, J = 7.6, 1H), 6.86 – 6.80 (m, 2H), 6.73 (s, 1H), 2.30 (s, 3H), 2.18 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.90, 154.00, 137.49, 131.49, 129.75, 127.25, 126.96, 125.39, 120.73, 118.51, 21.17, 15.92 ppm. IR (neat, cm^{-1}): 1486, 1254, 1223, 1116, 1091.



3-Chloro-2′,5′-dimethyldiphenylether Following the general procedure for Table 3, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 3-chlorophenol (63 μL, 0.6 mmol), bromo-*p*-xylene (69 μL, 0.5 mmol), K_3PO_4 (212 mg, 1 mmol), and 4Å mol. sieves (50 mg) in toluene (1 mL) was heated at 120°C for 24 h. The crude product was purified on a silica column eluting with hexanes to yield the title

compound as a clear oil (57 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (t, J = 8.1, 1H), 7.16 (d, J = 7.6, 1H), 7.04 – 7.00 (m, 1H), 6.95 (d, J = 7.6, 1H), 6.88 (t, J = 2.1, 1H), 6.82 – 6.76 (m, 2H), 2.32 (s, 3H), 2.18 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.17, 153.46, 137.57, 135.17, 131.53, 130.57, 127.17, 125.75, 122.39, 121.23, 117.26, 115.27, 21.17, 15.90 ppm. IR (neat, cm^{-1}): 1579, 1472, 1252, 1219, 1116.



2-Chloro-2′,5′-dimethyldiphenylether Following the general procedure for Table 3, a mixture of $[Pd(cinnamyl)Cl]_2$ (2.5 mg, 0.005 mmol), tBuBrettPhos (10 mg, 0.02 mmol), 2-chlorophenol (61 μL, 0.6 mmol), bromo-*p*-xylene (69 μL, 0.5 mmol), K_3PO_4 (212 mg, 1 mmol), and 4Å mol. sieves (50 mg) in toluene (1 mL) was heated at 120°C for 24 h. The crude product was purified on a silica column eluting with hexanes to yield the title compound as a clear oil (50 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (dd, J = 7.9, 1.5, 1H), 7.19 – 7.11 (m, 2H), 7.02 (td, J = 7.8, 1.4, 1H), 6.89 (d, J = 7.6, 1H), 6.76 (dd, J = 8.2, 1.3, 1H), 6.65 (s, 1H), 2.28 (s, 3H), 2.22 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.17, 153.47, 137.35, 131.40, 130.83, 127.94, 126.40, 125.10, 124.51, 123.61, 119.66, 118.58, 21.21, 15.88. IR (neat, cm^{-1}): 1507, 1478, 1256, 1115, 1059.

1.5 References

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Chapter 2. Pd-Catalyzed C-N Coupling: Ligand Structure Activity Relationships

2.1 Introduction

The development of palladium-catalyzed cross-coupling methods for carbon-heteroatom bond formation has had a broad impact on organic synthesis, and these methods were quickly adapted to use in the pharmaceuticals industry[1,2], natural product synthesis[3], materials chemistry[4], biological chemistry[5], and toxicology[6]. The rapid progress in this area is in part due to the design of new ligands and dialkylbiaryl phosphine ligands have proven particularly useful.[7]

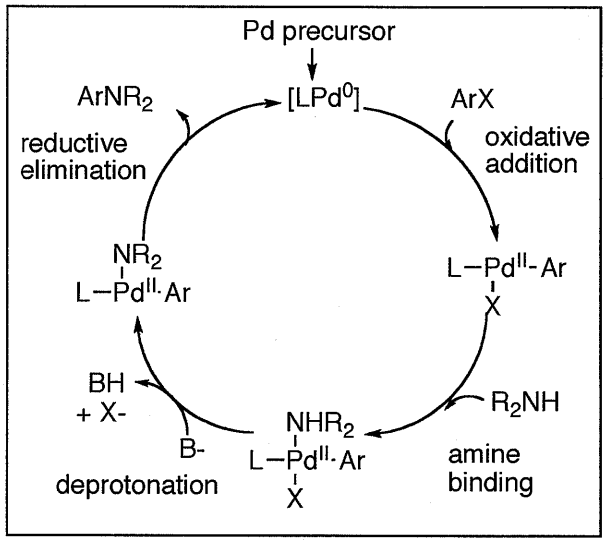


Figure 1. Proposed Catalytic Cycle for C-N Coupling

The mechanism of Pd-catalyzed C-N coupling has been extensively studied (Figure 1),[8-12] and some of the structural features of dialkylbiarylphosphine ligands that lead to increased catalyst reactivity and stability have been identified (Figure 2).[13-15] The catalytically active species in these reactions is believed to be a monophosphine Pd(0) complex [LPd^0], which is in equilibrium with the bisphosphine complex [L_2Pd^0].[16] Increasing the steric bulk of the ligand encourages formation of the [LPd^0] species, thereby increasing the concentration of catalytically active species. Oxidative addition of the aryl halide affords the $LPd^{II}(Ar)(X)$ complex. The strong electron-donating ability of

dialkylbiarylphosphine ligands facilitates oxidative addition by increasing the electron density at the metal center. A two-step transmetalation occurs, involving coordination of the amine followed by deprotonation of the N-H (which is acidified by binding of the amine to the Pd(II) center). Reductive elimination releases the N-aryl amine product and regenerates the active [Pd^0] species. Increasing steric bulk of the ligand enhances the rate of reductive elimination, and Pd-arene interactions with the non-phosphorous-containing aryl ring also aid in reductive elimination.[17]

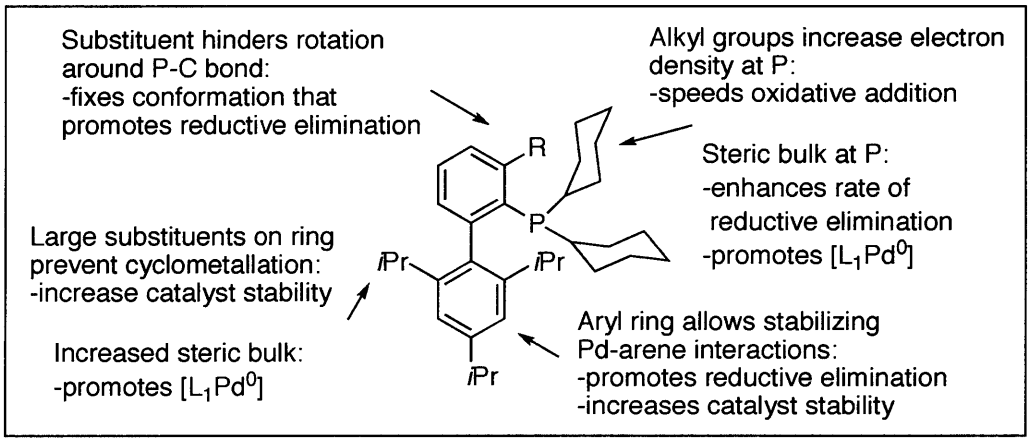


Figure 2. Important Structural Features of Dialkylbiarylphosphines

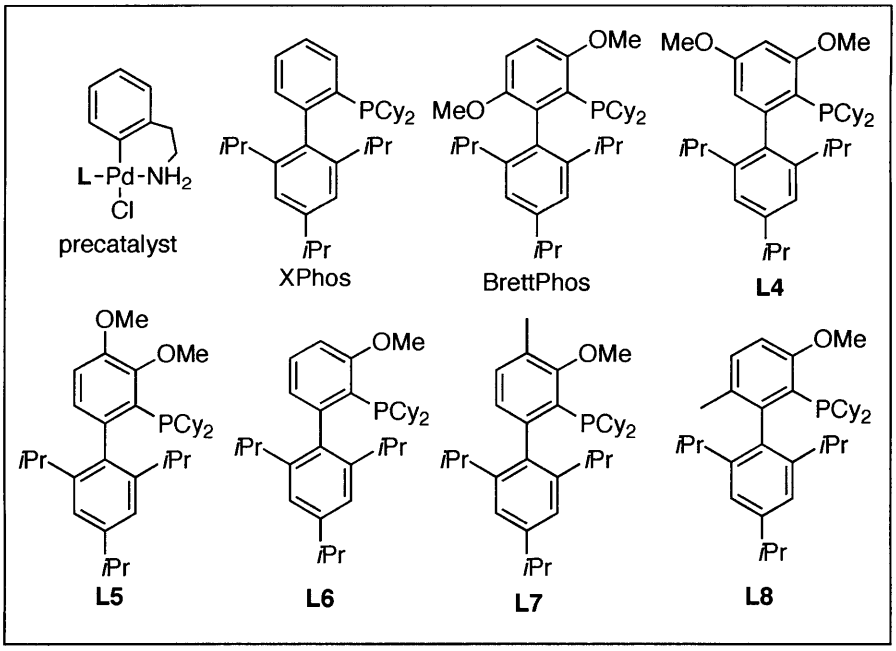


Figure 3. Ligands Evaluated in C-N Coupling Reactions

Recently a new ligand of this type was developed in the Buchwald laboratories, BrettPhos (Figure 3), and has been shown to produce a highly active and stable Pd catalyst for C-N coupling reactions.[18] In order to understand the origin of the unprecedented stability and reactivity of these catalysts, a structure-activity-relationship (SAR) study was undertaken. A series of related ligands (Figure 3) were synthesized and their efficacy in Pd-catalyzed C-N coupling reactions was compared.

2.2 Results and Discussion

Using a route analogous to that used for the synthesis of BrettPhos,[18] I synthesized ligands **L4-L8** (Figures 3, 4). The biaryl moiety of these ligands is synthesized via addition of a Grignard reagent to a benzyne, which is generated in-situ by ortho-lithiation of an aryl fluoride, followed by LiF elimination. I attempted to synthesize **L9-L10** (Figure 5), which cannot be accessed via the benzyne route, through a variety of cross-coupling routes, however, the extreme steric demands of this tris-*iso*-propylphenyl group make this a particularly challenging target, and all approaches thus far have failed to provide the desired ligand.

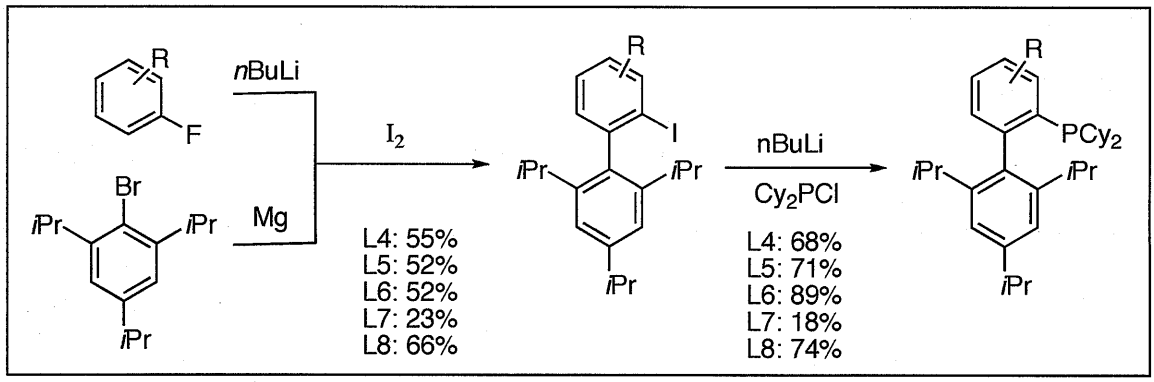


Figure 4. Synthesis of Ligands **L4-L8**

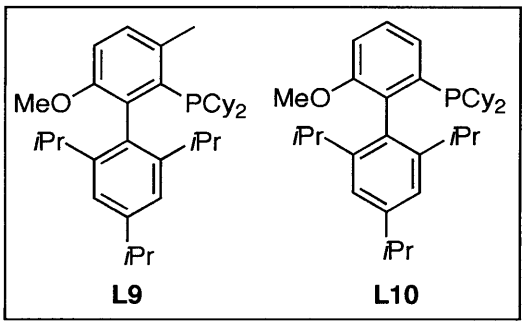


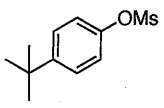
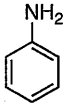
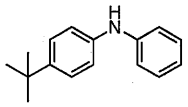
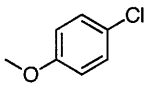
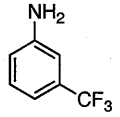
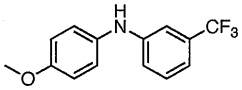
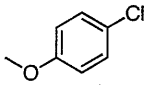
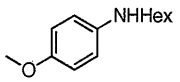
Figure 5. Ligands Not Accessible via the Benzyne Route

The series of ligands, **L4-L8**, was tested in a variety of C-N coupling reactions using different substrate classes (aryl mesylates, 1° alkyl amines, electron deficient anilines). Water pre-activation[19] of the $Pd(OAc)_2$ precursor was performed before addition of the reagents (Table 1). Evaluating the relative efficiencies of these ligands in cross-coupling reactions was complicated by the varying rates of ligand oxidation in the pre-activation step. In order to be more confident that the same amount of active catalyst was being generated in each reaction, I prepared the corresponding precatalysts[20] (Figure 3) for each of these ligands. Although **L5** forms an effective catalyst with $Pd(OAc)_2$, formation of the precatalyst with this ligand was unsuccessful, despite repeated attempts. Using water pre-activation the best results were obtained using BrettPhos followed by **L6**, however, reactions performed using the precatalysts indicated that **L4** was a more effective ligand than **L6** (Tables 1-2).

Pd catalysts containing BrettPhos are the only catalysts previously reported by the Buchwald group capable of efficiently coupling aryl mesylates and coupling methylamine with high selectivity for monoarylation.[7] Although coupling reactions using **L4-L8** are less efficient than when BrettPhos is used, the results are still much better than those obtained with other ligands (such as XPhos). Reactions with **L4-L8** also selectively form monoarylated products in the coupling of primary amines similar to cases where

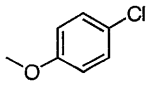
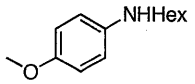
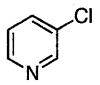
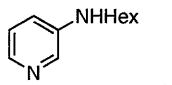
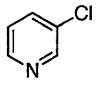
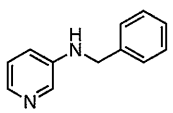
BrettPhos is used. The methoxy group *ortho* to phosphorous appears to be necessary to achieve this high selectivity for mono-arylation, indicated by the results with **L4-L8** and the fact that a ligand with a methyl group in that position is unable to achieve similar results.[18]

Table 1. C-N Coupling Reactions Performed with Water Pre-activation of $Pd(OAc)_2$

ArX	H_2NR	Product	Ligand	% Conversion	% GC Yield
			BrettPhos	90	89
			L4	25	20
			L5	25	19
			L6	70	64
			BrettPhos	100	100
			L4	86	75
			L5	100	93
			L6	100	99
	H_2NHex		BrettPhos	82	68[a]
			L4	32	20[a]
			L5	14	8[a]
			L6	84	61[a]

Reaction Conditions: ArX (1 mmol), H_2NR (1.2 mmol), K_2CO_3 (1.2 mmol), $Pd(OAc)_2$ (1 mol%), ligand (3 mol%), *t*BuOH (1 mL/mmol), 110°C, 1-6 h; GC yield based on dodecane internal standard. [a] Changes to above conditions: H_2NR (1.4 mmol), NaO*t*Bu (1.2 mmol), 85°C, 7 min.

Table 2. Coupling of 1° Alkyl Amines at Low Catalyst Loading (w/ precatalysts)

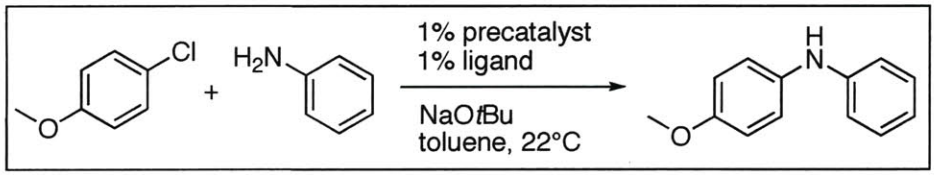
ArX	H_2NR	Product	Ligand	mol % Pd	% Conversion	% Yield
	H_2NHex		BrettPhos	0.05	100	90[a]
			L4	0.05	100	74[a]
			L6	0.05	86	66[a]
	H_2NHex		BrettPhos	0.10	100[b]	73[c]
			L4	0.20	88[b]	43[c]
			L6	0.25	59[b]	39[c]
	H_2NBn		BrettPhos	0.10	100[b]	84[c]
			L4	0.25	100[b]	80[c]
			L6	0.25	59[b]	39[c]
			L8	0.20	100[b]	81[c]

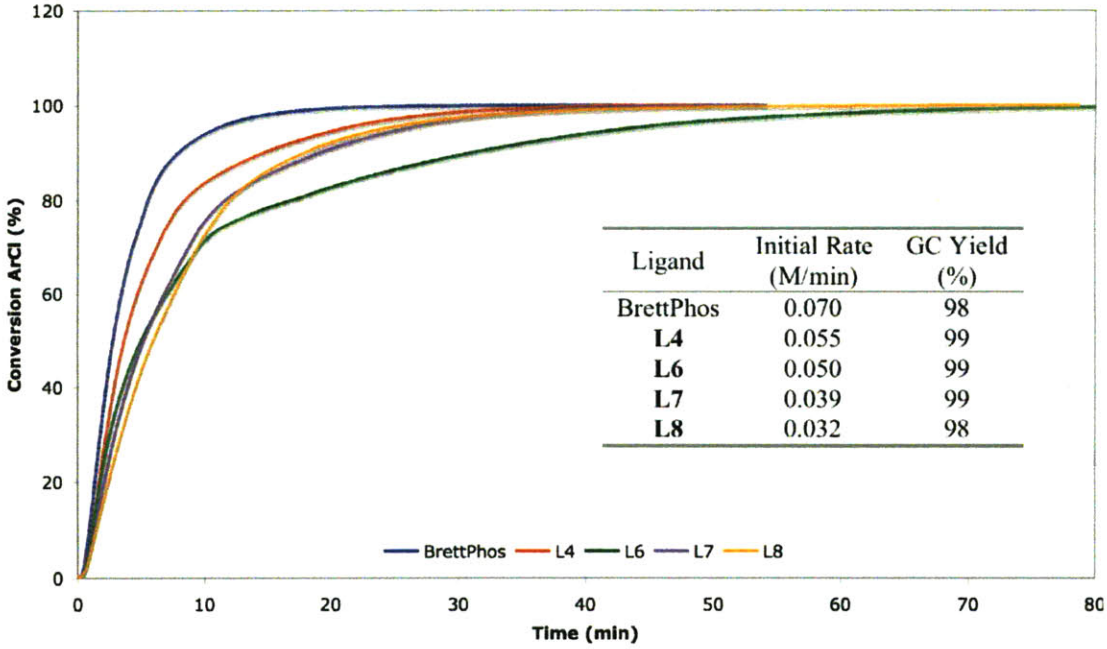
Reaction Conditions: ArX (1 mmol), H_2NR (1.4 mmol), NaO*t*Bu (1.2 mmol), 1:1 precatalyst:ligand, Bu_2O (1 mL/ mmol), 85°C, 1-5 h. [a] GC yield based on dodecane internal standard. [b] Percent conversion based on recovered aryl chloride. [c] Isolated yield.

Calorimetric studies were undertaken to compare the rates of cross-coupling for reactions performed with each ligand of this series (**L4-L8**). Coupling reactions of 4-chloroanisole with either aniline or methylamine were performed in a calorimeter, and

the results are shown in Figures 6-7. While the **L6** supported catalyst has a similar initial rate to BrettPhos and **L4**, this catalyst appears to have a significantly shorter lifetime, based on the much longer completion time (Figures 6-7), and on the results obtained when performing reactions with this ligand at low catalyst loadings (Table 2). The **L8** supported catalyst had the slowest initial rate of this series for the coupling of aniline, but is extremely efficient for the coupling of methylamine, surpassing the BrettPhos supported catalyst in reaction rate and yield. These results and the coupling of 3-chloropyridine with benzylamine in good yield with only 0.2% Pd in 1 h (Table 2) are very promising, and the use of catalysts containing **L8** for coupling primary alkyl amines merits further investigation.

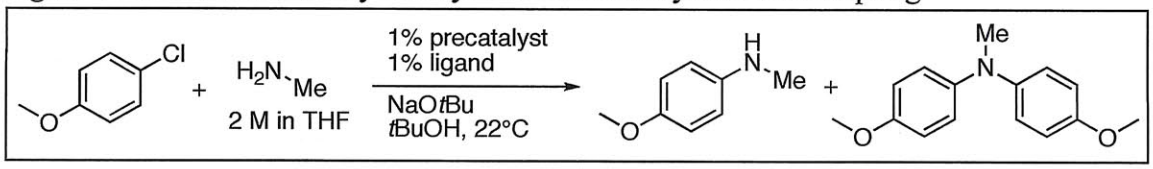
Figure 6. Calorimetric Study of Aryl Chloride Aniline Coupling

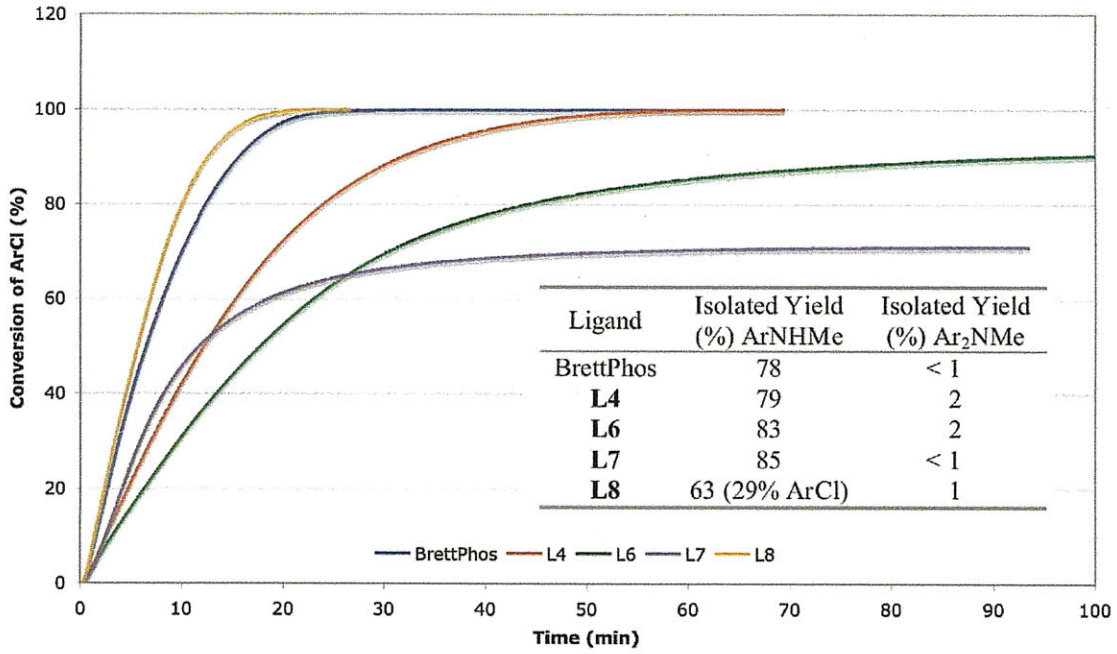




Ligand	Initial Rate (M/min)	GC Yield (%)
BrettPhos	0.070	98
L4	0.055	99
L6	0.050	99
L7	0.039	99
L8	0.032	98

Figure 7. Calorimetric Study of Aryl Chloride Methyl Amine Coupling





Ligand	Isolated Yield (%) ArNHMe	Isolated Yield (%) Ar_2NMe
BrettPhos	78	< 1
L4	79	2
L6	83	2
L7	85	< 1
L8	63 (29% ArCl)	1

2.3 Conclusions

A series of novel dialkylbiarylphosphine ligands was synthesized and their utility in Pd-catalyzed C-N couplings was investigated. The Pd-catalysts supported by these ligands are efficient at performing coupling reactions of aryl halides with primary alkyl or aryl amines, but cannot match the rates and low catalyst loadings achieved by BrettPhos-supported Pd catalysts. However, catalysts containing **L8** are extremely efficient for the coupling of methylamine, and merit further investigation. All of the ligands which posses a methoxy substituent *ortho* to the phosphorous atom generated catalysts which demonstrated high selectivities for monoarylation of primary alkyl amines, which suggests that the nature and position of this substituent is critical for regulating selectivity.

2.4 Experimental Section

General Reagent Information

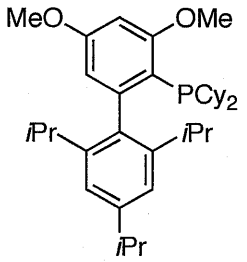
All reactions were carried out under an argon atmosphere in oven-dried resealable screw top test tubes or Schlenk tubes. $Pd(OAc)_2$ was a gift from BASF and $(CH_3CN)_2PdCl_2$ was a gift from Strem. $(TMEDA)PdMe_2$ was synthesized via literature procedure.[20] Aryl halides and amines were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics or TCI America. All amines and aryl chlorides that were liquids were distilled from calcium hydride and stored under argon. Amines and aryl halides that were solids were used as purchased without further purification. The 1,4-dimethoxyfluorobenzene was purchased from Synquest Labs, Inc. and used as received. Sodium *tert*-butoxide (Aldrich Chemical Co.) was stored in bulk in an N_2 glovebox. Small portions were taken outside the box in glass vials and weighed in the air. The methylamine solution, n-butyl and *t*-butyl lithium solutions, 1,4-dioxane, THF, and *tert*-butanol were purchased from Aldrich Chemical Co. in Sure-Seal bottles and were used as recieved. Dibutyl ether was purchased from Aldrich Chemical Co., anhydrous and was distilled from sodium metal. Toluene was obtained from J. T. Baker in CYCLE-TAINER kegs which were purged with argon for two hours and subsequently passed through two columns of neutral alumina and copper(II) oxide under a pressure of argon for further purification. The BrettPhos ligand and precatalyst were synthesized using literature procedures.[18] Silica column chromatography was performed using either Silicycle silica gel (ultra pure grade) or a Biotage SP4 Flash Purification System on KP-Sil silica cartridges.

General Analytical Information

Compounds were characterized by ^1H NMR, ^{13}C NMR, melting point, IR spectroscopy and, in certain cases, elemental analysis or high resolution mass spectrometry. (Copies of ^1H-NMR and ^{13}C NMR spectra are provided in Appendix A for all new compounds). Data of known compounds were compared with existing literature characterization data and the references are given. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument. The chemical shifts are reported in parts per million (ppm) based on the reference of the deuterated solvent. IR spectra were measured using a Perkin – Elmer 2000 FTIR (compounds were applied in a thin film on a KBr plate). All GC

analyses were performed on a Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). GC yields and conversions were reported as referenced to dodecane as an internal standard. GC-MS analyses were performed on an Agilent 6850 instrument with an Agilent 5975 inert Mass Selective Detector. Melting points (uncorrected) were measured using a Mel-Temp II capillary apparatus. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

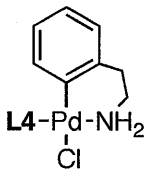
Ligand Syntheses



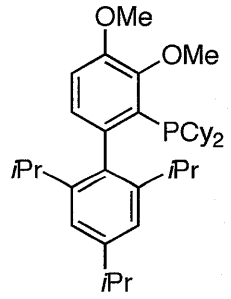
2-dicyclohexylphosphino-2',4',6'-triisopropyl-3,5-dimethoxybiphenyl (L4) An oven-dried three-neck 250 mL round bottom flask was equipped with a magnetic stir, fitted with a reflux condenser, glass stopper and rubber septum, and charged with magnesium shavings (737 mg, 30.72 mmol). The flask was purged with argon and then THF (55 mL), 1-bromo-2,4,6-triisopropylbenzene (7.25 g, 25.6 mmol), and 1,2-dibromoethane (40 μL) were added via syringe. The reaction mixture was heated at reflux for 1 h, and then allowed to cool to room temperature. A separate oven-dried 500 mL Schlenk flask, which was equipped with a magnetic stir bar and fitted with a septum, was purged with argon and then THF (80 mL) and 1-fluoro-3,5-dimethoxybenzene (2 g, 12.8 mmol) were added via syringe. The reaction vessel was cooled in a -78°C bath and n-BuLi (2.5 M in hexane, 5.12 mL, 12.8 mmol) was added dropwise via syringe. The solution was stirred for 30 min. followed by addition of the Grignard reagent (prepared in the first reaction vessel) via cannula over a 20 min. period. After the addition was complete, the cold bath was removed and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0°C and a solution of iodine in THF (1 M, 26 mL, 26 mmol) was added via cannula over 15 min. The mixture was allowed to warm to room temperature and stirred for 1 h. The excess I_2 was quenched by addition of saturated aqueous sodium sulfite until the dark red color disappeared. The resulting solution was

concentrated under reduced pressure, then extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was recrystallized from ethyl acetate to provide the desired biaryl iodide as white crystals. The mother liquor was concentrated and the remaining residue was recrystallized from ethyl acetate to yield additional white crystals, (3.26 g total, 55%), mp 170-173°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (s, 2H), 6.43 (d, J = 2.7, 1H), 6.41 (d, J = 2.7, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 2.95 (hept, J = 6.8, 1H), 2.44 (hept, J = 6.8, 2H), 1.30 (d, J = 6.8, 6H), 1.20 (d, J = 6.8, 6H), 1.04 (d, J = 6.8, 6H).

An oven-dried 100 mL Schlenk flask was equipped with a magnetic stir bar, charged with 2-iodo-2',4',6'-triisopropyl-3,5-dimethoxybiphenyl (1.25 g, 2.68 mmol), fitted with a septum, and purged with argon. THF (10 mL) was added and the solution was cooled to -78°C. n-BuLi (2.5 M in hexane, 1.2 mL, 2.95 mmol) was added dropwise via syringe and the reaction mixture was allowed to stir for 30 minutes, followed by addition of dicyclohexylchlorophosphine (652 mg, 2.8 mmol) via syringe. The reaction mixture was stirred at -78°C for 1 h, then allowed to warm to room temperature and stirred for an additional 1.5 h. The reaction mixture was filtered through a pad of silica over a pad of celite, eluting with ethyl acetate, then concentrated under reduced pressure. The yellow oily residue recrystallized from methanol to yield the title compound as a white powder (974 mg, 68%), mp 161-163°C. ^{1}H NMR (400 MHz, C_6D_6) δ: 7.24 (s, 2H), 6.39 (d, J= 6.5, 1H), 6.34 (d, J= 6.5, 1H), 3.31 (s, 3H), 3.25 (s, 3H), 2.90 (hept, J= 6.0, 3H), 2.44-2.32 (m, 2H), 2.03-1.95 (m, 2H), 1.80-1.64 (m, 8H), 1.51 (d, J= 6.0, 6H), 1.39-1.16 (m, 22H) ppm. ^{13}C NMR (101 MHz, C_6D_6) δ: 164.52, 164.49, 161.70, 161.69, 152.75, 152.37, 148.42, 146.51, 146.50, 139.25, 139.18, 121.01, 116.87, 116.59, 109.13, 109.06, 98.56, 55.15, 54.96, 37.83, 37.69, 35.10, 34.00, 33.75, 31.73, 31.63, 31.21, 28.87, 28.79, 28.36, 28.23, 27.36, 26.99, 24.78, 24.02 ppm. (Observed complexity is due to P-C splitting). ^{31}P NMR (161 MHz, C_6D_6) δ: -5.25 ppm. IR (neat, cm^{-1}): 2958, 2925, 2849, 1588, 1448, 1205, 1090. Anal. Calcd. for $C_{35}H_{53}O_2P$: C, 78.32; H, 9.95. Found: C, 78.12; H, 9.80.



L4 palladium(II) phenethylamine chloride (L4 precatalyst). An oven-dried 100 mL Schlenk flask, which was cooled under vacuum, was equipped with a magnetic stir bar, fitted with a septum, charged with (TMEDA)$PdMe_2$ (505 mg, 2 mmol) and **L4** (1.07 g, 2 mmol), and purged with argon. 2-(2-chlorophenyl)ethylamine (311 mg, 2 mmol) and MTBE (15 mL) were added via syringe. The reaction vessel was sealed with a teflon screw cap, and heated at 55°C for 2 h. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The brown solid was dissolved in a minimum amount of MTBE, layered with hexanes and allowed to sit for 18 h, during which time an off-white precipitate formed. The precipitate was collected by vacuum filtration and rinsed with cold MTBE to give the desired complex as an off-white powder (644 mg, 40%), ^{1}H NMR (400 MHz, C_6D_6) δ: Complex spectrum, see Appendix A. ^{31}P NMR (161 MHz, C_6D_6) δ: 48.50 ppm. IR (neat, cm^{-1}): 2931, 1592, 1448, 1324, 1207, 1026, 911, 731.

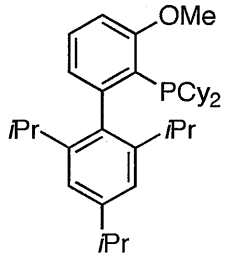


2-dicyclohexylphosphino-2',4',6'-triisopropyl-3,4-dimethoxybiphenyl (L5) An oven-dried three-neck 250 mL round bottom flask was equipped with a magnetic stir, fitted with a reflux condenser, glass stopper and rubber septum, and charged with magnesium shavings (737 mg, 30.72 mmol). The flask was purged with argon and then THF (55 mL), 1-bromo-2,4,6-triisopropylbenzene (7.25 g, 25.6 mmol), and 1,2-dibromoethane (40 μL) were added via syringe. The reaction mixture was heated at reflux for 1 h, and then allowed to cool to room temperature. A separate oven-dried 500 mL Schlenk flask, which was equipped with a magnetic stir bar and fitted with a septum, was purged with argon and then THF (80 mL) and 1,2-dimethoxy-4-fluorobenzene (2 g, 12.8 mmol) were

added via syringe. The reaction vessel was cooled in a -78°C bath and n-BuLi (2.5 M in hexane, 5.12 mL, 12.8 mmol) was added dropwise via syringe. The solution was stirred for 30 min. followed by addition of the Grignard reagent (prepared in the first reaction vessel) via cannula over a 20 min. period. After the addition was complete, the cold bath was removed and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0°C and a solution of iodine in THF (1 M, 26 mL, 26 mmol) was added via cannula over 15 min. The mixture was allowed to warm to room temperature and stirred for 1 h. The excess I_2 was quenched by addition of saturated aqueous sodium sulfite until the dark red color disappeared. The resulting solution was concentrated under reduced pressure, then extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The yellow oily residue was recrystallized from ethyl acetate to provide the desired biaryl iodide compound as white crystals, (3.11 g, 52%). NMR analysis indicated 20% impurity of the other regioisomer, but the compound was used directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (s, 2H), 6.92 (m, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 2.95 (hept, J = 6.9, 1H), 2.41 (hept, J = 6.9, 2H), 1.30 (d, J = 6.9, 6H), 1.19 (d, J = 6.9, 6H), 1.01 (d, J = 6.8, 6H) ppm.

An oven-dried 100 mL Schlenk flask was equipped with a magnetic stir bar, charged with 2-iodo-2',4',6'-triisopropyl-3,4-dimethoxybiphenyl (3.1 g, 6.65 mmol), fitted with a septum, and purged with argon. THF (30 mL) was added and the solution was cooled to -78°C. n-BuLi (2.5 M in hexane, 2.9 mL, 7.3 mmol) was added dropwise via syringe and the reaction mixture was allowed to stir for 30 min., followed by addition of dicyclohexylchlorophosphine (1.62 g, 6.98 mmol) via syringe. The reaction mixture was stirred at -78°C for 1 h, then allowed to warm to room temperature and stirred for an additional 1.5 h. The reaction mixture was filtered through a pad of silica over a pad of celite, eluting with ethyl acetate, then concentrated under reduced pressure. The yellow oily residue was recrystallized from methanol to yield the title compound as a white powder (2.55 g, 71%), mp 194-196°C. ^{1}H NMR (400 MHz, C_6D_6) δ: 7.26 (s, 2H), 6.90 (dd, J = 8.3, 3.8, 1H), 6.52 (d, J = 8.3, 1H), 3.88 (s, 3H), 3.26 (s, 3H), 2.97 – 2.83 (m, 3H), 2.47 – 2.34 (m, 2H), 2.04 – 1.96 (m, 2H), 1.86 – 1.78 (m, 2H), 1.74 – 1.59 (m, 6H), 1.51 (d, J = 6.8, 6H), 1.37 – 1.15 (m, 22H) ppm. ^{13}C NMR (101 MHz, C_6D_6) δ: 153.09,

153.06, 151.12, 148.42, 147.23, 142.48, 142.12, 138.73, 138.66, 130.11, 129.79, 127.14, 127.07, 120.94, 113.77, 60.79, 55.34, 38.06, 37.91, 35.09, 33.89, 33.64, 31.85, 31.76, 31.30, 28.47, 28.39, 28.21, 28.08, 27.23, 26.88, 24.78, 23.88 ppm. (Observed complexity is due to P-C splitting). ^{31}P NMR (161 MHz, C_6D_6) δ: 0.94 ppm. IR (neat, cm^{-1}): 2929, 2849, 1462, 1284, 1008. Anal. Calcd. for $C_{35}H_{53}O_2P$: C, 78.32; H, 9.95. Found: C, 78.23; H, 9.97.

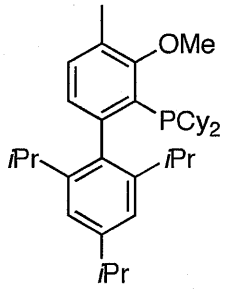


2-Dicyclohexylphosphino-2',4',6'-triisopropyl-3-methoxybiphenyl (L6) An oven-dried three-neck 500 mL round bottom flask was equipped with a magnetic stir, fitted with a reflux condenser, glass stopper and rubber septum, and charged with magnesium shavings (1.83 g, 76 mmol). The flask was purged with argon and then THF (100 mL), 1-bromo-2,4,6-triisopropylbenzene (17.95 g, 63.4 mmol), and 1,2-dibromoethane (40 μL) were added via syringe. The reaction mixture was heated at reflux for 1 h, and then allowed to cool to room temperature. A separate oven-dried 500 mL Schlenk flask, which was equipped with a magnetic stir bar and fitted with a septum, was purged with argon and then THF (160 mL) and 1-fluoro-3-methoxybenzene (4 g, 31.7 mmol) were added via syringe. The reaction vessel was cooled in a -78°C bath and n-BuLi (2.5 M in hexane, 12.7 mL, 31.7 mmol) was added dropwise via syringe. The solution was stirred for 30 min. followed by addition of the Grignard reagent (prepared in the first reaction vessel) via cannula over a 20 min. period. After the addition was complete, the cold bath was removed and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0°C and a solution of iodine in THF (1 M, 64 mL, 64 mmol) was added via cannula over 15 min. The mixture was allowed to warm to room temperature and stirred for 1 h. The excess I_2 was quenched by addition of saturated aqueous sodium sulfite until the dark red color disappeared. The resulting solution was concentrated under reduced pressure, then extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered,

and concentrated under reduced pressure. The crude material was recrystallized from ethyl acetate to provide the desired biaryl iodide as white crystals. The mother liquor was concentrated and the remaining residue was recrystallized from ethyl acetate to yield additional white crystals, (7.24 g total, 52%), mp 125-127°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (t, J = 7.8, 1H), 7.08 (s, 2H), 6.86 (dd, J = 7.5, 1.3, 1H), 6.80 (dd, J = 8.2, 1.1, 1H), 3.96 (s, 2H), 2.98 (hept, J = 7.0, 1H), 2.43 (hept, J = 6.8, 2H), 1.34 (d, J = 6.9, 6H), 1.23 (d, J = 6.9, 6H), 1.04 (d, J = 6.8, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.35, 148.53, 148.08, 145.75, 139.49, 128.79, 123.33, 120.90, 108.75, 94.29, 56.56, 34.35, 30.77, 25.19, 24.28, 23.69 ppm. Anal. Calcd. for $C_{22}H_{29}IO$: C, 60.55; H, 6.70. Found: C, 60.53; H, 6.78.

An oven-dried 200 mL Schlenk flask was equipped with a magnetic stir bar, charged with 2-iodo-2',4',6'-triisopropyl-3-methoxybiphenyl (5 g, 11.46 mmol), fitted with a septum, and purged with argon. THF (50 mL) was added and the solution was cooled to -78°C. n-BuLi (2.5 M in hexane, 5 mL, 12.6 mmol) was added dropwise via syringe and the reaction mixture was allowed to stir for 30 min., followed by addition of dicyclohexylchlorophosphine (2.8 g, 12.03 mmol) via syringe. The reaction mixture was stirred at -78°C for 1 h, then allowed to warm to room temperature and stirred for an additional 1.5 h. The reaction mixture was filtered through a pad of silica over a pad of celite, eluting with ethyl acetate, then concentrated under reduced pressure. The crude product was recrystallized from acetone to yield the title compound as a white powder (5.17 g, 89%), mp 160-162°C. ^{1}H NMR (400 MHz, C_6D_6) δ: 7.24 (s, 2H), 7.07 (t, J = 8.0, 1H), 6.90 (dd, J = 8.0, 3.3, 1H), 6.41 (d, J = 8.0, 1H), 3.31 (s, 3H), 2.86 (hept, J = 6.9, 3H), 2.45 – 2.33 (m, 2H), 2.02-1.94 (m, 2H), 1.76-1.62 (m, 8H), 1.48 (d, J = 6.8, 6H), 1.40 – 1.08 (m, 22H) ppm. ^{13}C NMR (101 MHz, C_6D_6) δ: 163.32, 163.29, 151.70, 151.34, 148.44, 146.67, 146.65, 138.79, 138.71, 129.99, 125.47, 125.41, 125.11, 120.94, 109.63, 55.03, 37.56, 37.41, 35.07, 33.82, 33.58, 31.80, 31.70, 31.26, 28.79, 28.71, 28.32, 28.18, 27.30, 26.77, 24.76, 23.87 ppm. (Observed complexity is due to P-C splitting). ^{31}P NMR (161 MHz, C_6D_6) δ: -3.06 ppm. IR (neat, cm^{-1}): 2959, 2925, 2849, 1561, 1453, 1246, 1020, 794. Anal. Calcd. for $C_{34}H_{51}OP$: C, 80.59; H, 10.14. Found: C, 80.66; H, 10.15.

L6 palladium(II) phenethylamine chloride (L6 precatalyst). An oven-dried 100 mL Schlenk flask, which was cooled under vacuum, was equipped with a magnetic stir bar, fitted with a septum, charged with (TMEDA)$PdMe_2$ (800 mg, 3.17 mmol) and **L6** (1.6 g, 3.17 mmol), and purged with argon. 2-(2-chlorophenyl)ethylamine (493 mg, 3.17 mmol) and MTBE (20 mL) were added via syringe. The reaction vessel was sealed with a teflon screw cap, and heated at 55°C for 3 h. Then the reaction mixture was cooled to 0°C during which time a white precipitate formed. The precipitate was collected by vacuum filtration and rinsed with cold MTBE to give the desired complex as a white powder (1.93 g, 71%). ^{1}H NMR (400 MHz, C_6D_6) δ: Complex spectrum, see Appendix A. ^{31}P NMR (161 MHz, C_6D_6) δ: 50.56 ppm. IR (neat, cm^{-1}): 2930, 1560, 1449, 1265, 1016, 911, 732.



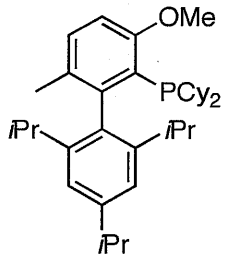
2-dicyclohexylphosphino-2',4',6'-triisopropyl-3-methoxy-4-methylbiphenyl (L7) An oven-dried three-neck 250 mL round bottom flask was equipped with a magnetic stir, fitted with a reflux condenser, glass stopper and rubber septum, and charged with magnesium shavings (816 mg, 34 mmol). The flask was purged with argon and then THF (50 mL), 1-bromo-2,4,6-triisopropylbenzene (8.1 g, 28.6 mmol), and 1,2-dibromoethane (30 μL) were added via syringe. The reaction mixture was heated at reflux for 1 h, and then allowed to cool to room temperature. A separate oven-dried 500 mL Schlenk flask, which was equipped with a magnetic stir bar and fitted with a septum, was purged with argon and then THF (80 mL) and 5-fluoro-2-methylanisole (2 g, 14.3 mmol) were added via syringe. The reaction vessel was cooled in a -78°C bath and n-BuLi (2.5 M in hexane, 5.7 mL, 14.3 mmol) was added dropwise via syringe. The

solution was stirred for 30 min. followed by addition of the Grignard reagent (prepared in the first reaction vessel) via cannula over 20 min. After the addition was complete, the cold bath was removed and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0°C and a solution of iodine in THF (1 M, 29 mL, 29 mmol) was added via cannula over 15 min. The mixture was allowed to warm to room temperature and stirred for 1 h. The excess I_2 was quenched by addition of saturated aqueous sodium sulfite until the dark red color disappeared. The resulting mixture was filtered, eluting with ethyl acetate to remove precipitated salts, concentrated under reduced pressure, then extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica column eluting with a gradient of 0-10% ethyl acetate in hexanes to yield the biaryl iodide as a waxy white solid (1.5 g, 23%). NMR analysis indicated small amounts of impurities, but the compound was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, J = 7.6, 1H), 7.04 (s, 2H), 6.86 (d, J = 7.6, 1H), 3.83 (s, 3H), 2.95-2.91 (m, 1H), 2.42 (s, 3H), 2.40-2.35 (m, 2H), 1.30 (d, J = 6.9, 6H), 1.20 (d, J = 6.9, 6H), 1.00 (d, J = 6.8, 6H).

An oven-dried 100 mL Schlenk flask was equipped with a magnetic stir bar, charged with 2-iodo-2',4',6'-triisopropyl-3-methoxy-4-methylbiphenyl (1.25 g, 2.78 mmol), fitted with a septum, and purged with argon. THF (12 mL) was added and the solution was cooled to -78°C. n-BuLi (2.5 M in hexane, 1.2 mL, 3.06 mmol) was added dropwise via syringe and the reaction mixture was allowed to stir for 30 min., followed by addition of dicyclohexylchlorophosphine (675 mg, 2.9 mmol) via syringe. The reaction mixture was stirred at -78°C for 1 h, then allowed to warm to room temperature and stirred for an additional 1.5 h. The reaction mixture was filtered through a pad of silica over a pad of celite, eluting with ethyl acetate, then concentrated under reduced pressure. The yellow oily residue was recrystallized from ethanol to yield the title compound as white crystals (255 mg, 18%), mp 151-155°C. ^{1}H NMR (400 MHz, C_6D_6) δ: 7.24 (s, 2H), 6.96 – 6.88 (m, 2H), 3.48 (s, 3H), 2.93 – 2.80 (m, 3H), 2.39 – 2.29 (m, 2H), 2.08 (s, 3H), 2.03 – 1.96 (m, 2H), 1.81 – 1.60 (m, 8H), 1.50 (d, J = 6.8, 6H), 1.35 – 1.13 (m, 22H) ppm. ^{13}C NMR (101 MHz, C_6D_6) δ: 163.53, 163.49, 149.25, 148.89, 148.42, 146.83, 138.92, 138.84, 133.22, 129.57, 129.26, 128.32, 127.94, 127.87, 120.95, 60.68, 38.31, 38.16, 35.07,

33.94, 33.69, 31.86, 31.76, 31.30, 28.46, 28.38, 28.22, 28.08, 27.22, 26.84, 24.76, 23.82, 18.39 ppm. (Observed complexity is due to P-C splitting). ^{31}P NMR (161 MHz, C_6D_6) δ: -0.40 ppm. IR (neat, cm^{-1}): 2958, 2926, 2850, 1449, 1360, 1252, 1011. Anal. Calcd. for $C_{35}H_{53}OP$: C, 80.72; H, 10.26. Found: C, 80.62; H, 10.37.

L7 palladium(II) phenethylamine chloride (L7 precatalyst). An oven-dried 25 mL Schlenk flask, which was cooled under vacuum, was equipped with a magnetic stir bar, fitted with a septum, charged with (TMEDA)$PdMe_2$ (73 mg, 0.29 mmol) and **L7** (150 mg, 0.29 mmol), and purged with argon. 2-(2-chlorophenyl)ethylamine (45 mg, 0.29 mmol) and MTBE (3 mL) were added via syringe. The reaction vessel was sealed with a teflon screw cap, and heated at 55°C for 2 h. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The brown solid was dissolved in a minimum amount of MTBE, layered with hexanes and allowed to sit for 18 h, during which time a white precipitate formed. The precipitate was collected by vacuum filtration and rinsed with cold MTBE to give the desired complex as an off-white powder (150 mg, 60%), ^{1}H NMR (400 MHz, CD_2Cl_2) δ: Complex spectrum, see Appendix A. ^{31}P NMR (161 MHz, CD_2Cl_2) δ: 42.88 ppm. IR (neat, cm^{-1}): 2930, 1559, 1457, 1258, 996, 732.



2-dicyclohexylbiphenyl-2',4',6'-triisopropyl-3-methoxy-6-methylbiphenyl (L8) An oven-dried three-neck 250 mL round bottom flask was equipped with a magnetic stir, fitted with a reflux condenser, glass stopper and rubber septum, and charged with magnesium shavings (1 g, 42.72 mmol). The flask was purged with argon and then THF (65 mL), 1-bromo-2,4,6-triisopropylbenzene (10.08 g, 35.6 mmol), and 1,2-

dibromoethane (40 μL) were added via syringe. The reaction mixture was heated at reflux for 1 h, and then allowed to cool to room temperature. A separate oven-dried 500 mL Schlenk flask, which was equipped with a magnetic stir bar and fitted with a septum, was purged with argon and then THF (100 mL) and 3-fluoro-4-methylanisole (2.5 g, 17.8 mmol) were added via syringe. The reaction vessel was cooled in a -78°C bath and n-BuLi (2.5 M in hexane, 7.12 mL, 17.8 mmol) was added dropwise via syringe. The solution was stirred for 30 min. followed by addition of the Grignard reagent (prepared in the first reaction vessel) via cannula over 20 min. After the addition was complete, the cold bath was removed and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0°C and a solution of iodine in THF (1 M, 36 mL, 36 mmol) was added via cannula over 15 min. The mixture was allowed to warm to room temperature and stirred for 1 h. The excess I_2 was quenched by addition of saturated aqueous sodium sulfite until the dark red color disappeared. The reaction mixture was filtered to remove precipitates, and the filtrate was concentrated under reduced pressure. Water was added to the remaining yellow oil, and this mixture was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified via silica column eluting with a gradient of 0-10% ethyl acetate in hexanes to yield the title compound as a white solid, (5.28 g, 66%), mp 138-140°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (d, J = 8.0, 1H), 7.07 (s, 2H), 6.74 (d, J = 8.0, 1H), 3.92 (s, 3H), 2.97 (hept, J = 6.8, 1H), 2.35 (hept, J = 6.8, 2H), 1.99 (s, 3H), 1.32 (d, J = 6.8, 6H), 1.21 (d, J = 6.8, 6H), 1.06 (d, J = 6.8, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.57, 148.56, 146.83, 145.25, 138.66, 130.79, 130.32, 121.29, 109.24, 95.13, 56.54, 34.30, 30.77, 24.73, 24.70, 24.31, 21.48 ppm. Anal. Calcd. for $C_{23}H_{31}IO$: C, 61.33; H, 6.94. Found: C, 61.24; H, 6.92.

An oven-dried 50 mL Schlenk flask was equipped with a magnetic stir bar, charged with 2-iodo-2',4',6'-triisopropyl-3-methoxy-6-methylbiphenyl (850 mg, 1.89 mmol), fitted with a septum, and purged with argon. THF (10 mL) was added and the solution was cooled to -78°C. n-BuLi (2.5 M in hexane, 840 μL, 2.08 mmol) was added dropwise via syringe and the reaction mixture was allowed to stir for 30 min., followed by addition of dicyclohexylchlorophosphine (460 mg, 1.98 mmol) via syringe. The reaction mixture

was stirred at -78°C for 1 h, then allowed to warm to room temperature and stirred for an additional 1.5 h. The reaction mixture was filtered through a pad of silica over a pad of celite, eluting with ethyl acetate, then concentrated under reduced pressure. The crude product was recrystallized from acetone to yield the title compound as white crystals (733 mg, 74%), mp 157-159°C. ^{1}H NMR (400 MHz, C_6D_6) δ: 7.23 (s, 2H), 7.90 (d, J = 8.0, 1H), 6.44 (d, J = 8.0, 1H), 3.33 (s, 3H), 2.88 (hept, J = 6.8, 1H), 2.76 (hept, J = 6.8, 2H), 2.43-2.33 (m, 2H), 2.08-2.01 (m, 2H), 1.90 (s, 3H), 1.78-1.63 (m, 8H), 1.47 (d, J = 6.8, 6H), 1.42-1.12 (m, 22H) ppm. ^{13}C NMR (101 MHz, C_6D_6) δ: 161.38, 161.36, 150.51, 150.15, 148.35, 146.28, 137.46, 137.37, 132.63, 130.78, 130.71, 125.73, 125.44, 121.47, 109.68, 54.95, 37.88, 37.72, 34.94, 33.74, 33.52, 32.05, 31.93, 31.11, 28.96, 28.87, 28.46, 28.33, 27.32, 25.59, 25.55, 25.53, 24.72, 21.77, 21.74 ppm. (Observed complexity is due to P-C splitting). ^{31}P NMR (161 MHz, C_6D_6) δ: -2.07 ppm. IR (neat, cm^{-1}): 2925, 2850, 1566, 1459, 1264, 1020, 807. A satisfactory elemental analysis was not obtained for this compound.

L8 palladium(II) phenethylamine chloride (L8 precatalyst). An oven-dried 25 mL Schlenk flask, which was cooled under vacuum, was equipped with a magnetic stir bar, fitted with a septum, charged with (TMEDA)$PdMe_2$ (217 mg, 0.86 mmol) and **L8** (450 mg, 0.86 mmol), and purged with argon. 2-(2-chlorophenyl)ethylamine (134 mg, 0.86 mmol) and MTBE (6 mL) were added via syringe. The reaction vessel was sealed with a teflon screw cap, and heated at 55°C for 2 h. The reaction mixture was cooled in an ice bath, then filtered to collect the precipitate, which was washed with cold MTBE then with hexanes to give the desired complex as an off-white powder (495 mg, 66%), ^{1}H NMR (400 MHz, C_6D_6) δ: Complex spectrum, see Appendix A. ^{31}P NMR (161 MHz, C_6D_6) δ: 48.84 ppm. IR (neat, cm^{-1}): 2932, 1560, 1458, 1283, 1014, 926, 729.

General Procedure for Examples Described in Table 1

An oven-dried screw-top tube, which was equipped with a magnetic stir bar and fitted

with a teflon septum, was charged with $Pd(OAc)_2$ (1 mol%) and ligand (3 mol%). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and *t*BuOH (2 mL) and degassed H_2O (4 mol%) were added via syringe. After addition of the water, the solution was heated to 110 °C for 1.5 min.

A second oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a teflon septum, was charged with base (1.4 mmol) (aryl halides or amines that were solids at room temperature were added with the base). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and then the aryl halide (1.0 mmol) and amine (1.2 mmol) were added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second via cannula. The solution was heated to 110 °C for 1-6 h. The reaction mixture was then cooled to room temperature and dodecane (1.0 mmol) was added as an internal standard. The reaction mixture was then diluted with ethyl acetate, washed with water, and analyzed by GC.

General Procedure for Examples Described in Table 2

An oven-dried screw-top tube with a teflon septum was cooled to room temperature under argon pressure. The tube was charged with NaO*t*Bu (1.2 mmol), then the vessel was evacuated and backfilled with argon (this process was repeated a total of three times). The aryl chloride (1 mmol), amine (1.4 mmol), and dibutyl ether (1 mL) were added via syringe through the septum. Then the appropriate amount for the desired catalyst loading of a toluene solution (0.002 M) containing the ligand and corresponding precatalyst was added. [The ligand/Pd solution was prepared in an oven-dried screw-top 5 mL volumetric flask with a teflon septum. After addition of the ligand (0.01 mmol) and precatalyst (0.01 mmol), the flask was evacuated and backfilled with argon, this procedure was repeated three times, followed by addition of toluene (5mL)]. The reaction mixture was then heated at 85°C for 1-5 h. The reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate, washed with water, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

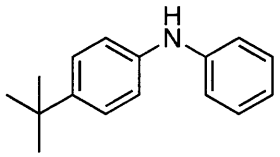
General Procedure for Calorimetric Studies - Aniline Coupling (Figure 6)

An oven-dried 16 mL vial was equipped with a magnetic stir bar, fitted with a screw-cap Teflon septum, and taken into the glovebox. Once in the glovebox, the vial was charged with NaO*t*Bu (115 mg, 1.2 mmol), 4-chloroanisole (122 μL, 1 mmol), aniline (110 μL, 1.2 mmol) and toluene (3 mL). The reaction mixture was then taken out of the glovebox and placed in an Omnical CRC reaction calorimeter along with a syringe containing a solution of the ligand and precatalyst in toluene (300 μL, 1 mol% precatalyst, 1 mol% ligand). The calorimeter was set to 22.4 °C and allowed to thermally equilibrate. After equilibration, the solution of ligand/precatalyst was injected and the reaction was stirred until the heat flow on the calorimeter returned to the baseline. A correction was then applied to the raw data due to the delay between the moment that the heat is given off of the reaction and the moment that it is detected. The corrected heat flow curve was then converted to rate by using the equation $q = \Delta H_{rxn} \cdot V \cdot r$, where q is the heat flow, ΔH_{rxn} is the heat of reaction, V is the reaction volume, and r is the reaction rate. The heat of reaction was found by integrating the heat flow vs. time curves, which gave an average of 190.8 J/mol for all 5 reactions. The corrected heat flow was converted to fractional conversion by dividing the area under the curve to any point by the total area under the curve.

General Procedure for Calorimetric Studies – Methylamine Coupling (Figure 7)

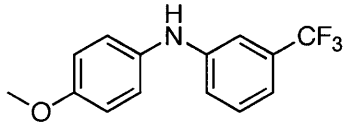
An oven-dried 16 mL vial was equipped with a magnetic stir bar, fitted with a screw-cap Teflon septum, and taken into the glovebox. Once in the glovebox, the vial was charged with NaO*t*Bu (115 mg, 1.2 mmol), 4-chloroanisole (122 μL, 1 mmol), and *t*BuOH (1 mL). The vial was taken out of the glovebox and methylamine solution (2 M in THF, 1 mL, 2 mmol) was added via syringe. The reaction mixture was then placed in an Omnical CRC reaction calorimeter along with a syringe containing a solution of the precatalyst and ligand in toluene (300 μL, 1 mol% precatalyst, 1 mol% ligand). The calorimeter was set to 22.4°C and allowed to thermally equilibrate. After equilibration, the solution of ligand/precatalyst was injected and the reaction was stirred until the heat flow on the calorimeter returned to the baseline. A correction was then applied to the raw data due to the delay between the moment that the heat is given off of the reaction and the

moment that it is detected. The corrected heat flow curve was then converted to fractional conversion by dividing the area under the curve to any point by the total area under the curve.



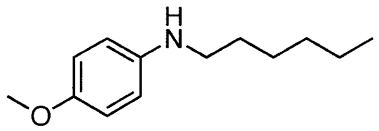
4-*tert*-butyl-*N*-phenylaniline[21]

The general procedure for Table 1 was used with the following modification: 5 mL *t*BuOH was added prior to the addition of the activated catalyst solution. A mixture of $Pd(OAc)_2$ (0.005 mmol), ligand (0.015 mmol), H_2O (1 μL), 4-*tert*-butylphenylmesylate (114 mg, 0.5 mmol), aniline (55 μL, 0.6 mmol), and K_2CO_3 (97 mg, 0.7 mmol) in *t*BuOH (6 mL) was heated at 110°C for 6 h. For the reaction run with **L6**, the crude product was purified on a silica column eluting with 0-15% ethyl acetate/ hexanes to afford the title compound as a white solid (45 mg, 40%), mp 68-70°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 – 7.28 (m, 2H), 7.27 – 7.22 (m, 2H), 7.07 – 7.01 (m, 4H), 6.89 (dd, J = 10.5, 4.2, 1H), 5.64 (bs, 1H), 1.31 (s, 9H) ppm. IR (neat, cm^{-1}): 3387, 1595, 1498, 1305, 744, 688.



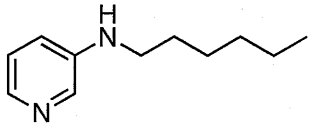
***N*-(4-methoxyphenyl)-3-(trifluoromethyl)aniline[20]**

Following the general procedure for Table 1, a mixture of $Pd(OAc)_2$ (0.01 mmol), ligand (0.03 mmol), H_2O (1 μL), 4-chloroanisole (122 μL, 1 mmol), 3-(trifluoromethyl)aniline (150 μL, 1.2 mmol), and K_2CO_3 (193 mg, 1.4 mmol) in *t*BuOH (2 mL) was heated at 110°C for 1 h. For the reaction run with **L6**, the crude product was purified on a silica column eluting with 0-25% ethyl acetate/ hexanes to afford the title compound as a white solid (247 mg, 92%), mp 56-58°C (lit.[20] mp 56-58°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 – 7.25 (m, 1H), 7.12-7.05 (m, 3H), 7.05 – 6.98 (m, 2H), 6.93 – 6.87 (m, 2H), 5.63 (bs, 1H), 3.82 (s, 3H) ppm. IR (neat, cm^{-1}): 3367, 1617, 1506, 1337, 1111, 920, 786, 700.

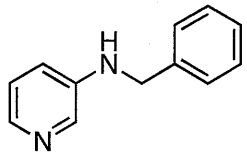


N-hexyl-4-methoxyaniline[18]

Following the general procedure for Table 1, a mixture of $Pd(OAc)_2$ (0.01 mmol), ligand (0.03 mmol), H_2O (1 μL), 4-chloroanisole (122 μL, 1 mmol), hexylamine (185 μL, 1.4 mmol), and NaO*t*Bu (115 mg, 1.2 mmol) in *t*BuOH (2 mL) was heated at 85°C for 7 min. Following the general procedure for Table 2, a mixture of NaO*t*Bu (115 mg, 1.2 mmol), hexylamine (185 μL, 1.4 mmol), 4-chloroanisole (122 μL, 1 mmol), and ligand/ precatalyst solution in dibutyl ether (1 mL) was heated at 85°C for 5 h. For the reaction run with BrettPhos, the crude product was purified on a silica column eluting with 0-15% ethyl acetate/hexanes to provide the title compound as a yellow oil (126 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.81 – 6.75 (m, 2H), 6.61 – 6.55 (m, 2H), 3.75 (s, 3H), 3.33 (bs, 1H), 3.05 (t, J = 7.1, 2H), 1.64 – 1.55 (m, 2H), 1.44 – 1.26 (m, 6H), 0.90 (t, J = 6.9, 3H) ppm. IR (neat, cm^{-1}): 3393, 2929, 2857, 1514, 1236, 1040, 818.

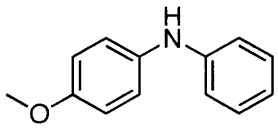


***N*-hexylpyridin-3-amine**[22] Following the general procedure for Table 2, a mixture of NaO*t*Bu (115 mg, 1.2 mmol), hexylamine (185 μL, 1.4 mmol), 3-chloropyridine (94 μL, 1 mmol), and ligand/precatalyst solution in dibutyl ether (1 mL) was heated at 85°C for 1 h. The crude product was purified on a silica column eluting with a gradient of 10-20% solution A in hexanes (solution A= 5% Et_3N, 10% *i*PrOH, 85% EtOAc) to yield the title compound as a white solid, mp 57-59°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 2.8, 1H), 7.94 (dd, J = 4.7, 1.3, 1H), 7.07 (dd, J = 8.3, 4.7, 1H), 6.85 (ddd, J = 8.3, 2.9, 1.3, 1H), 3.65 (bs, 1H), 3.11 (dd, J = 12.8, 7.0, 2H), 1.67 – 1.57 (m, 2H), 1.45 – 1.24 (m, 6H), 0.94 – 0.85 (m, 3H) ppm. IR (neat, cm^{-1}): 3256, 2928, 1593, 1476, 790, 705.

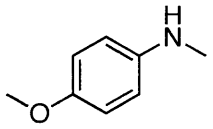


N-benzylpyridin-3-amine[23] Following the general procedure for Table 2, a mixture of NaO*t*Bu (115 mg, 1.2 mmol), benzylamine (153 μL, 1.4 mmol), 3-chloropyridine (94 μL, 1 mmol), and ligand/precatalyst solution in dibutyl ether (1 mL) was heated at 85°C for 1 h. The crude product was purified on a silica column eluting with a gradient of 10-20%

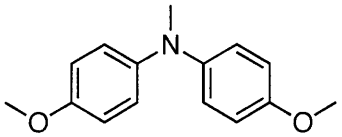
solution A in hexanes (Solution A= 5% Et_3N, 10% *i*PrOH, 85% EtOAc) to yield the title compound as an off-white solid, mp 87-89°C. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, J = 2.9, 1H), 7.97 (dd, J = 4.7, 1.2, 1H), 7.39 – 7.27 (m, 5H), 7.07 (dd, J = 8.3, 4.7, 1H), 6.88 (ddd, J = 8.3, 2.9, 1.3, 1H), 4.35 (d, J = 5.2, 2H), 4.17 (bs, 1H) ppm. IR (neat, cm^{-1}): 3263, 3031, 1591, 1485, 1297, 698.



N-phenyl-4-methoxyaniline[20] After running each reaction in the calorimeter as described in the general procedure for Figure 6, dodecane internal standard was added, and then the reaction mixture was diluted with ethyl acetate, washed with water, and analyzed by GC. (GC yields reported in Figure 6). The crude product from the reaction with **L7** was purified on a silica column eluting with 0-20% ethyl acetate/hexanes to yield the title compound as a white solid (179 mg, 90%), mp 106-108°C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.8, 2H), 7.11 – 7.05 (m, 2H), 6.93 – 6.81 (m, 5H), 5.50 (bs, 1H), 3.80 (s, 3H) ppm. IR (neat, cm^{-1}): 3389, 1597, 1516, 1249, 1034.



4-methoxy-N-methylaniline[18] After running each reaction in the calorimeter as described in the general procedure for Figure 7, the reaction mixture was diluted with ethyl acetate, and washed with water. The water layer was extracted with ethyl acetate and then the combined organic layers were concentrated and the residue was purified on a silica column eluting with a gradient of 5-50% ethyl acetate/hexanes. The product was isolated as a pale yellow oil in the yields shown in Figure 7. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.83 – 6.78 (m, 2H), 6.62 – 6.57 (m, 2H), 3.75 (s, 3H), 3.45 (bs, 1H), 2.81 (s, 3H) ppm. IR (neat, cm^{-1}): 3404, 2933, 1515, 1236, 1033, 819.



4-Methoxy-*N*-(4-methoxyphenyl)-*N*-methylaniline[18] This compound was isolated as a minor side product of the reactions described in the general procedure for Figure 7. ^1H

NMR (400 MHz, $CDCl_3$) δ: 6.93 – 6.89 (m, 4H), 6.85 – 6.80 (m, 4H), 3.78 (s, 6H), 3.21 (s, 3H) ppm.

2.5 References

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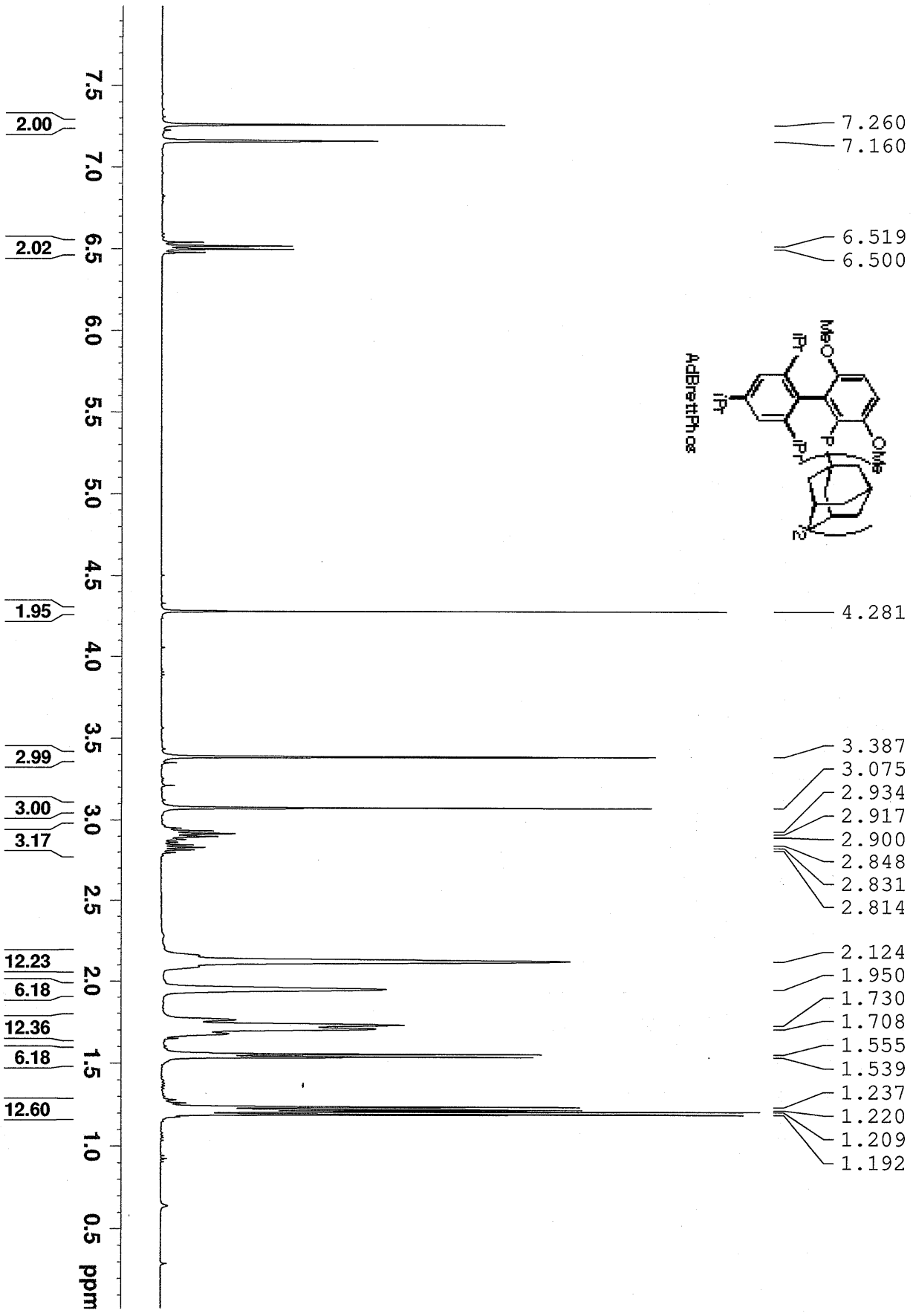
Appendix A. Selected NMR Spectra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2.124
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1.708
1.555
1.539
1.237
1.220
1.209
1.192
2.00
2.02
1.95
2.99
3.00
3.17
12.23
6.18
12.36
6.18
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6.5
6.0
5.5
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3.5
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2.5
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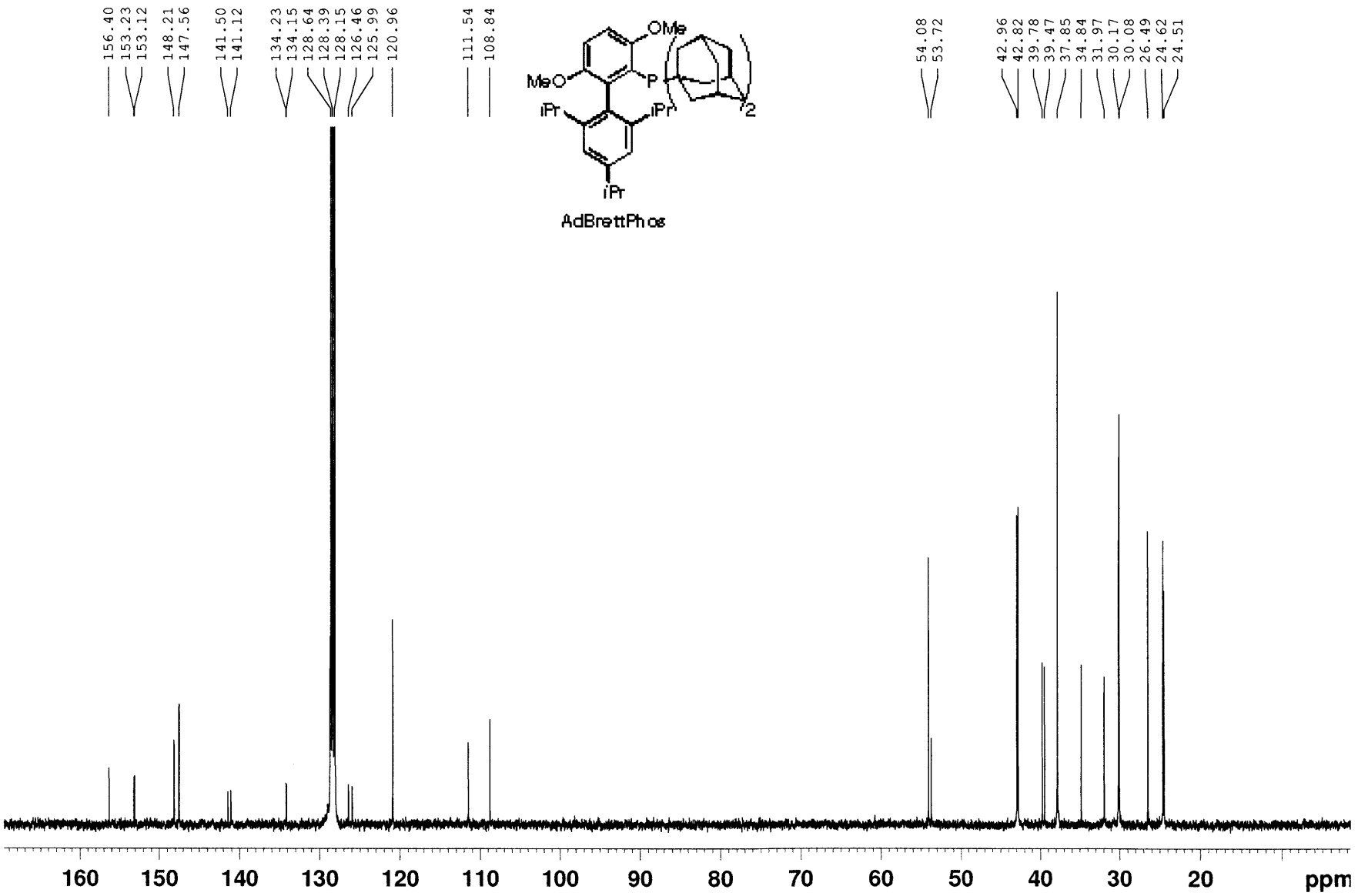
iPr
iPr
P
OMe
Pd
Cl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125.99
120.96
111.54
108.84
54.08
53.72
42.96
42.82
39.78
39.47
37.85
34.84
31.97
30.17
30.08
26.49
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24.51
OMe
MeO
P
iPr
iPr
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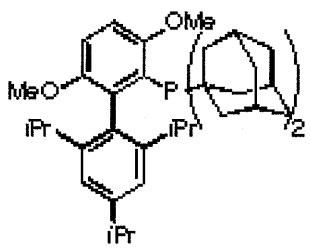

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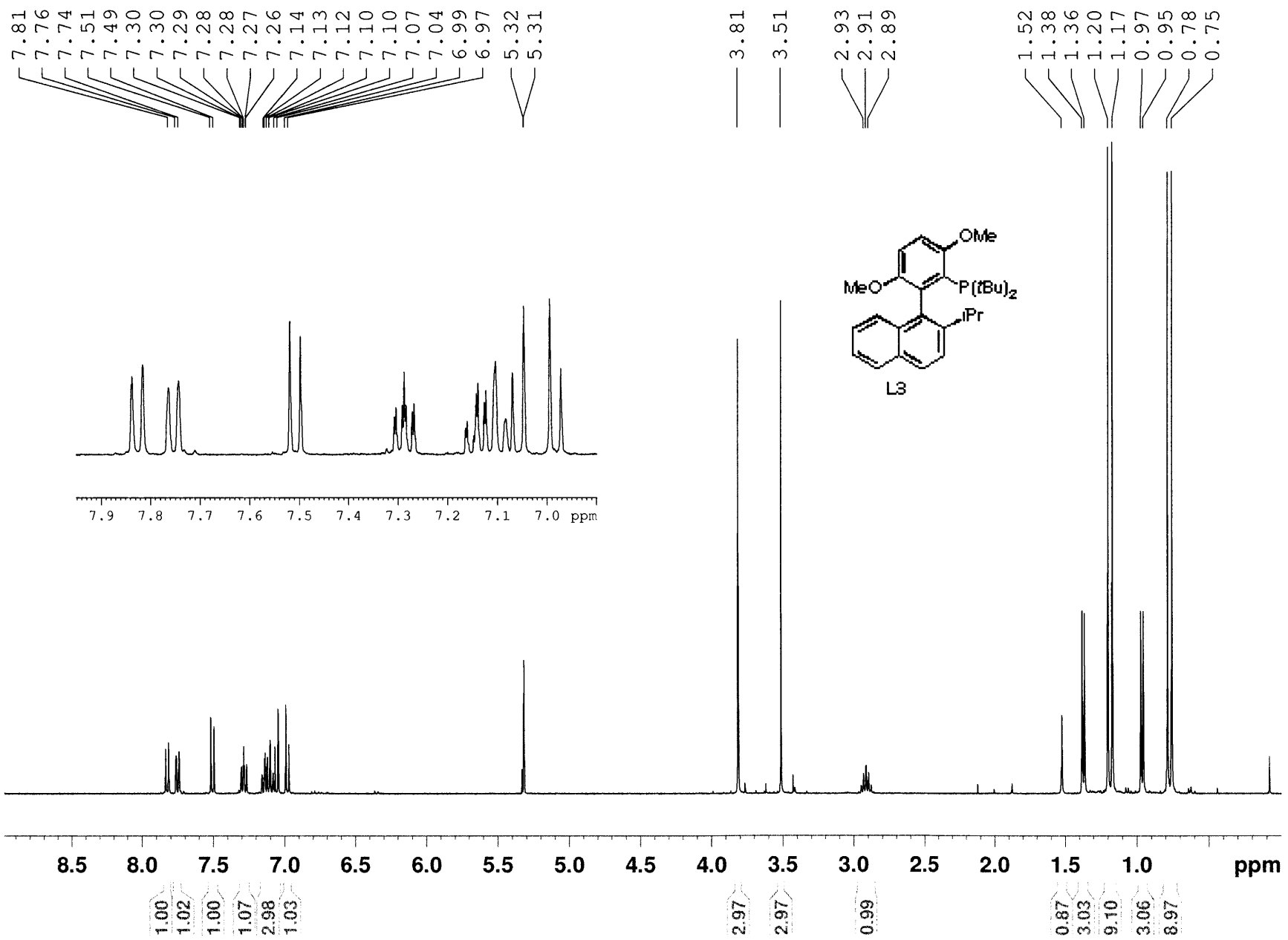
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5.31
3.81
3.51
2.93
2.91
2.89
1.52
1.38
1.36
1.20
1.17
0.97
0.95
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0.75
OMe
MeO
P(tBu)2
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L3
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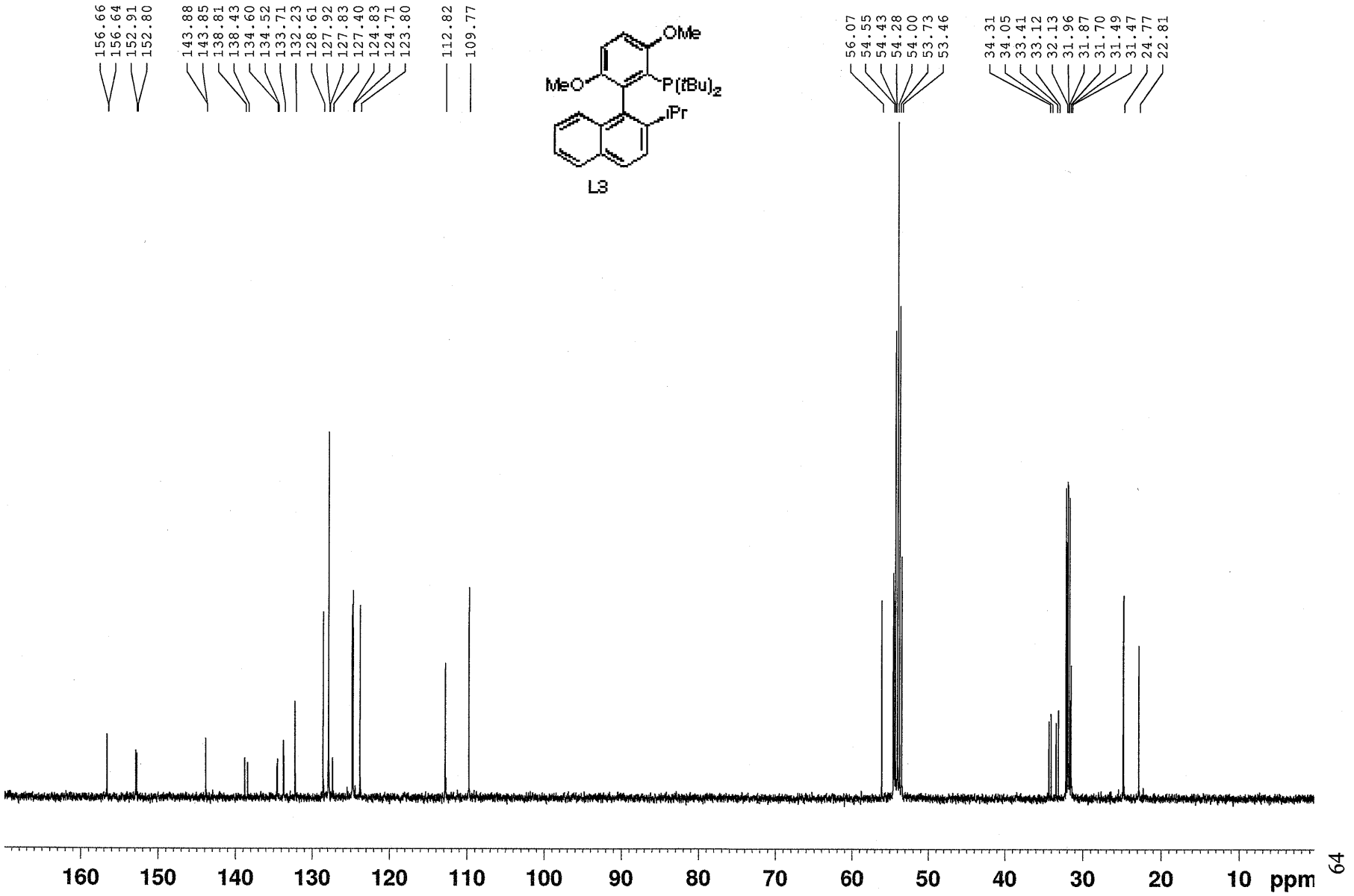
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140
130
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100
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70
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30
20
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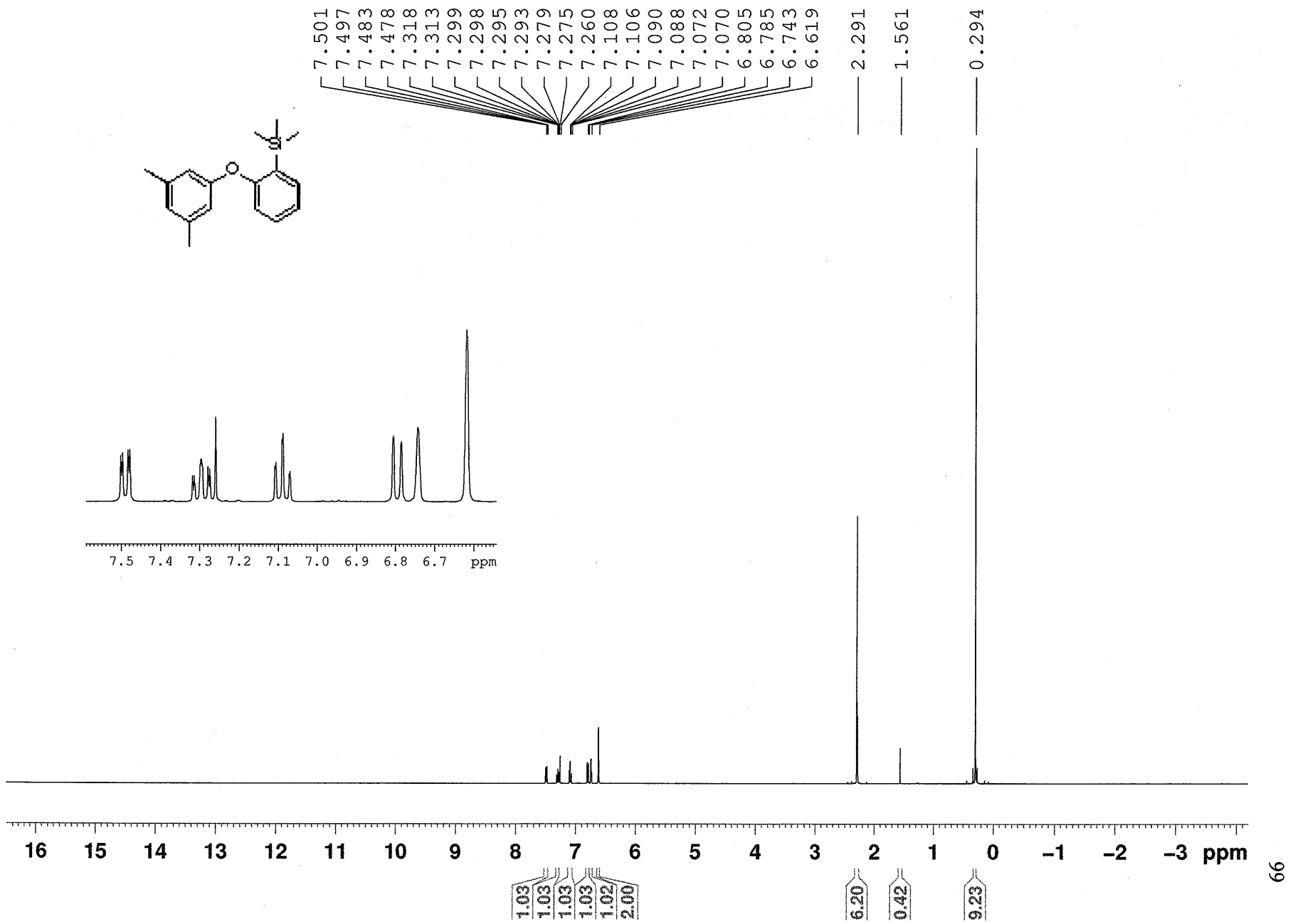
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7.106
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7.088
7.072
7.070
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6.785
6.743
6.619
2.291
1.561
0.294
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16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3 ppm
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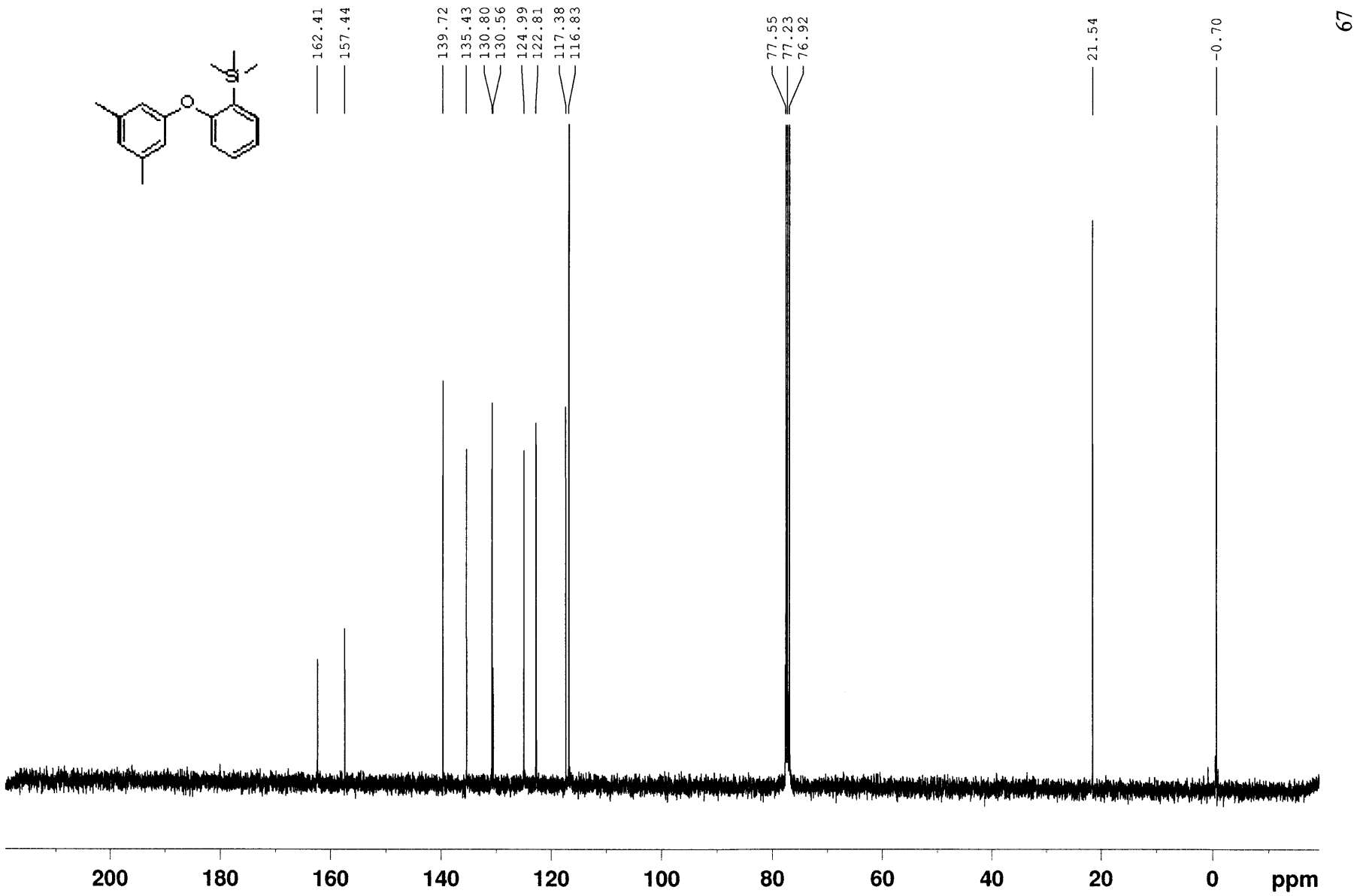
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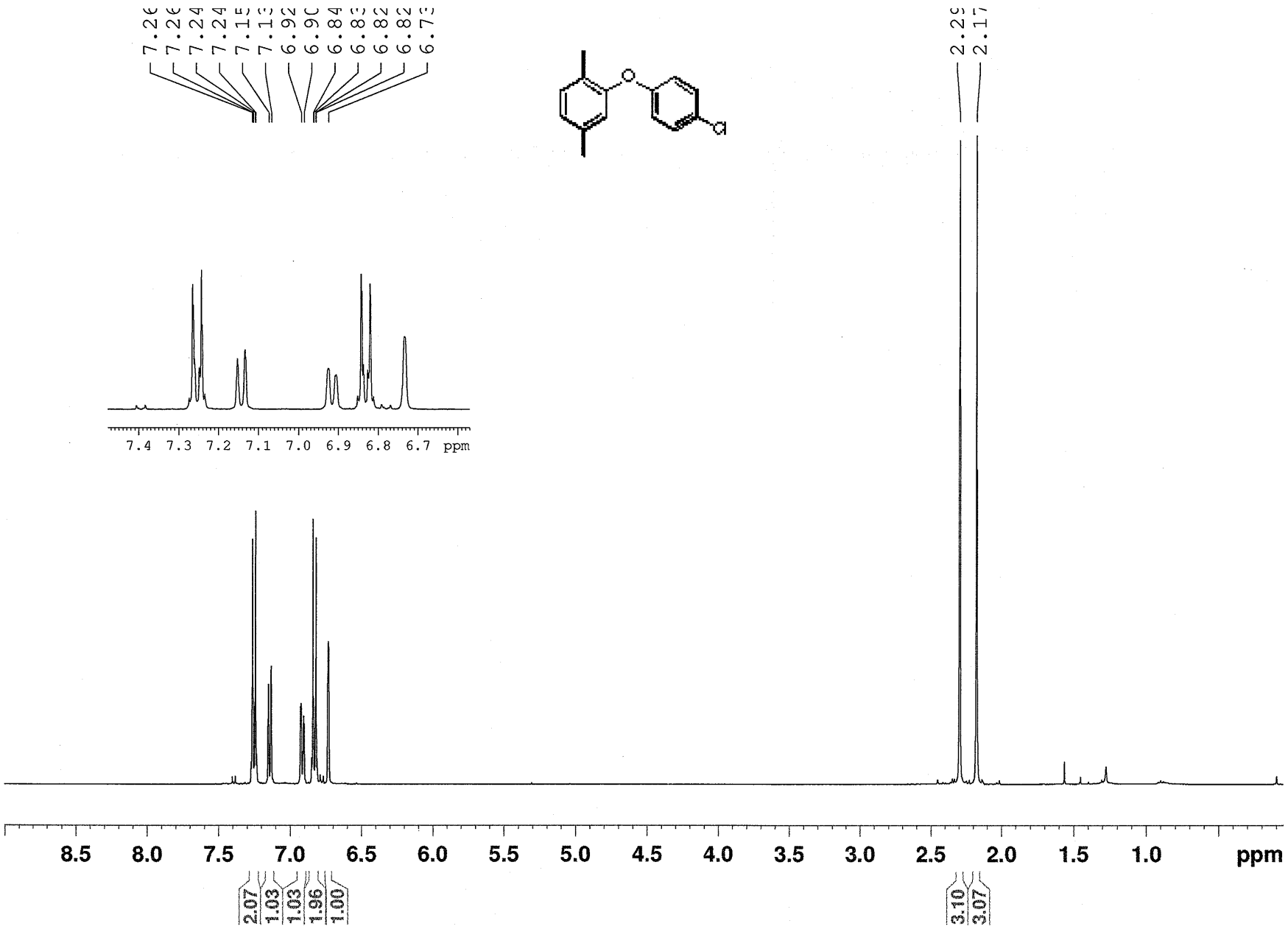
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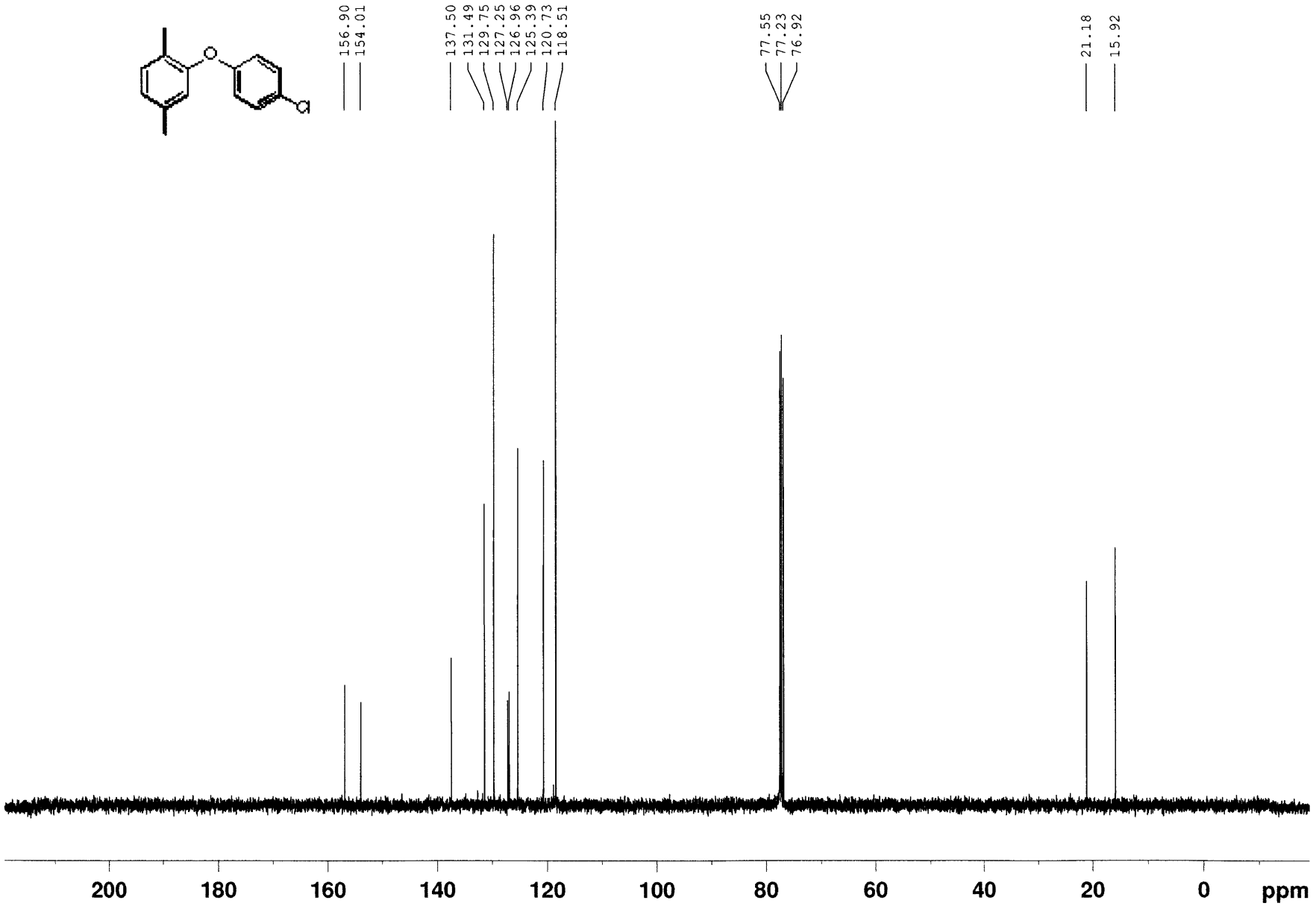
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125.39
120.73
118.51
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21.18
15.92
200
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120
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40
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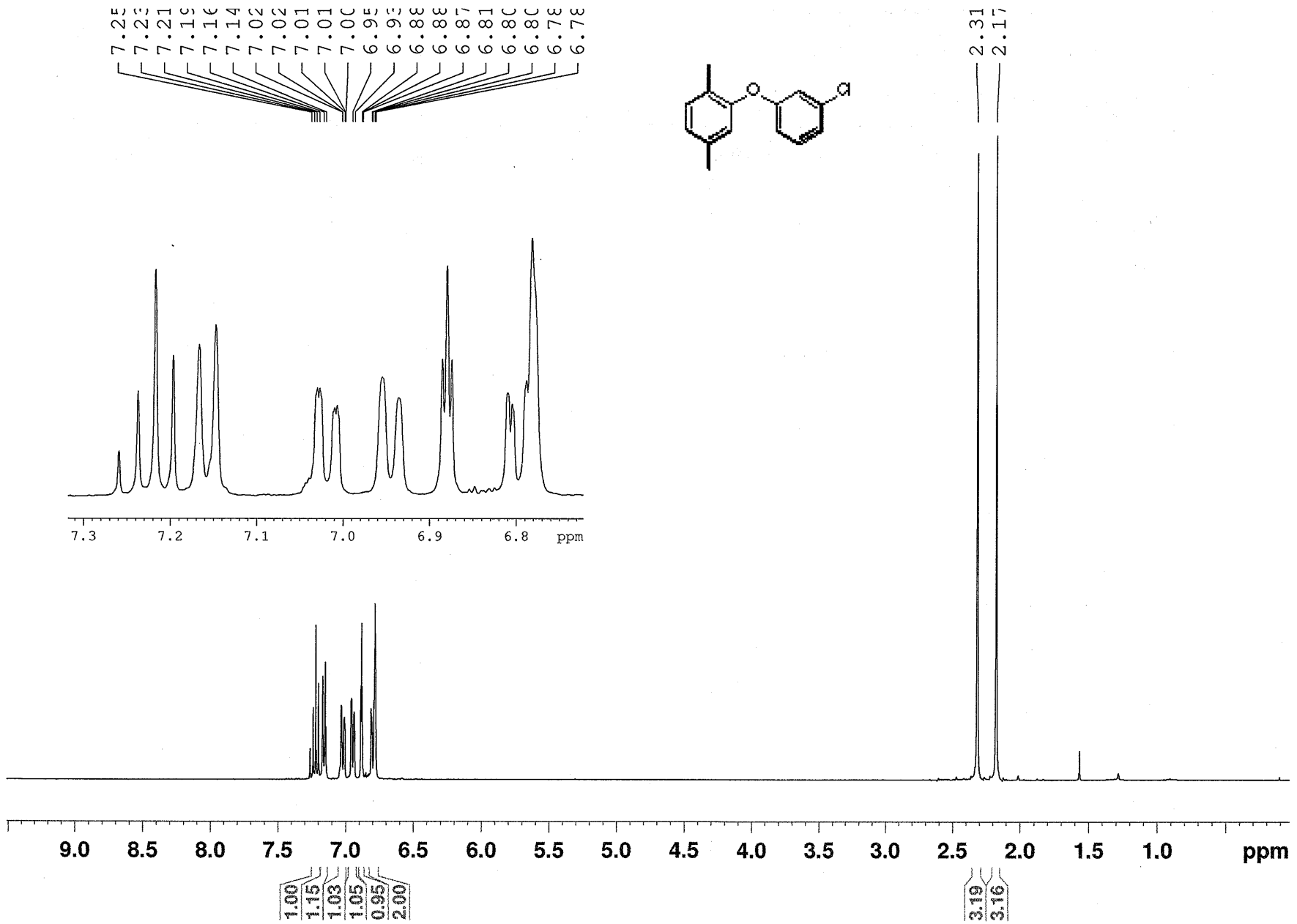
0
ppm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7.23
7.21
7.19
7.16
7.14
7.02
7.02
7.01
7.01
7.00
6.95
6.93
6.88
6.88
6.87
6.81
6.80
6.80
6.78
6.78
2.31
2.17
O
Cl
7.3
7.2
7.1
7.0
6.9
6.8
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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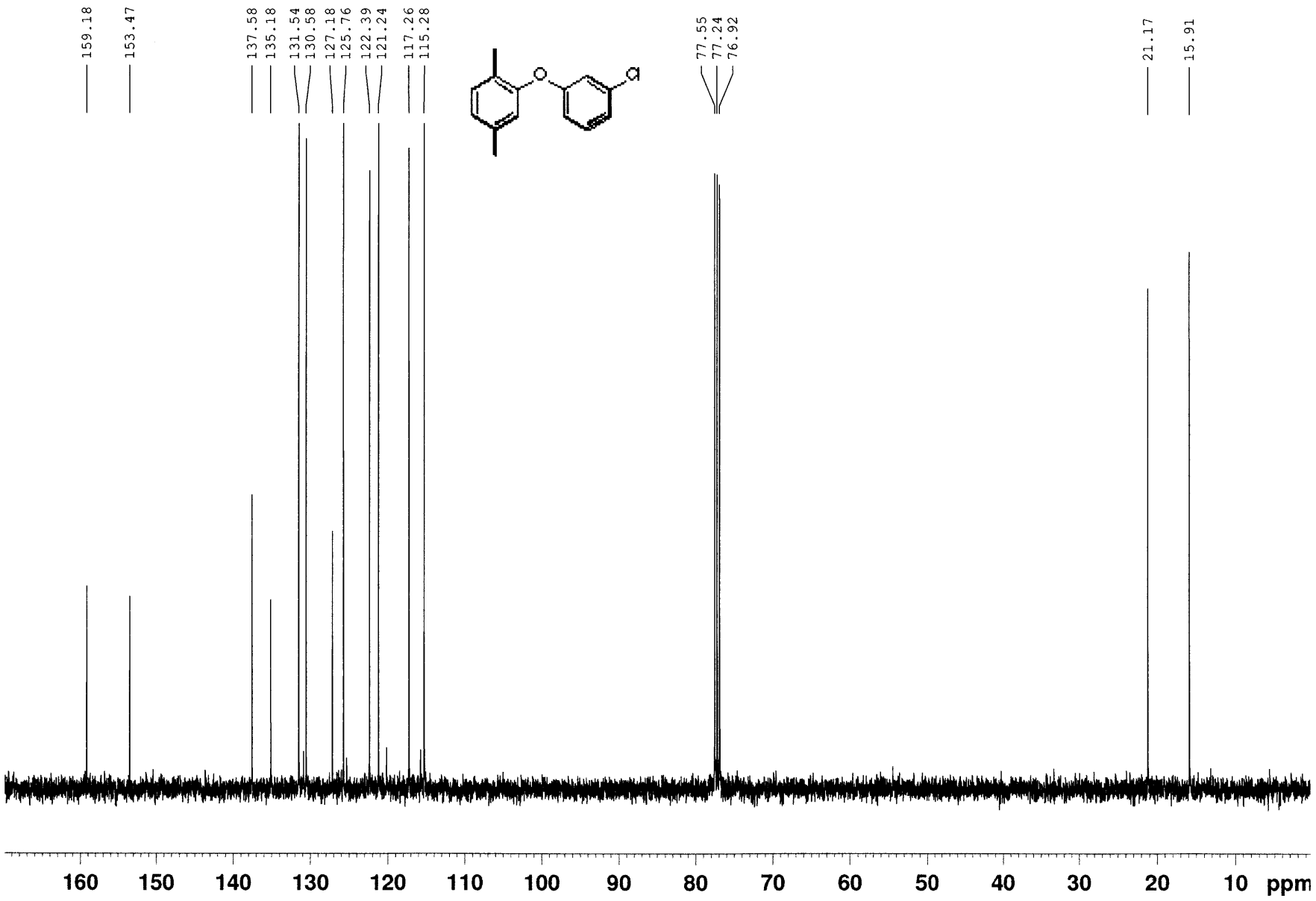
1.05
0.95
2.00
3.19
3.16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137.58
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130.58
127.18
125.76
122.39
121.24
117.26
115.28
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77.24
76.92
21.17
15.91
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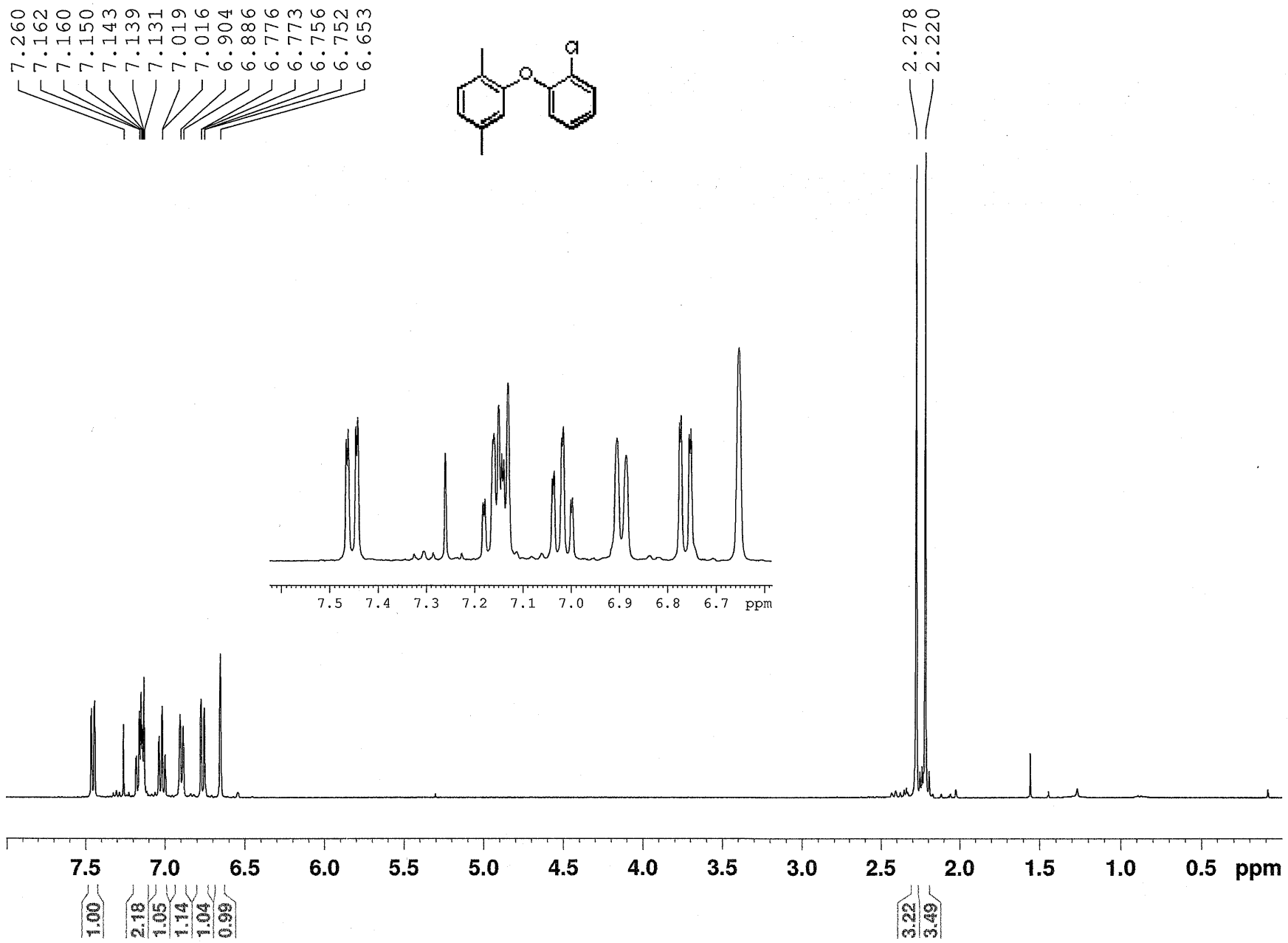
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.162
7.160
7.150
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7.139
7.131
7.019
7.016
6.904
6.886
6.776
6.773
6.756
6.752
6.653
Cl
O
2.278
2.220
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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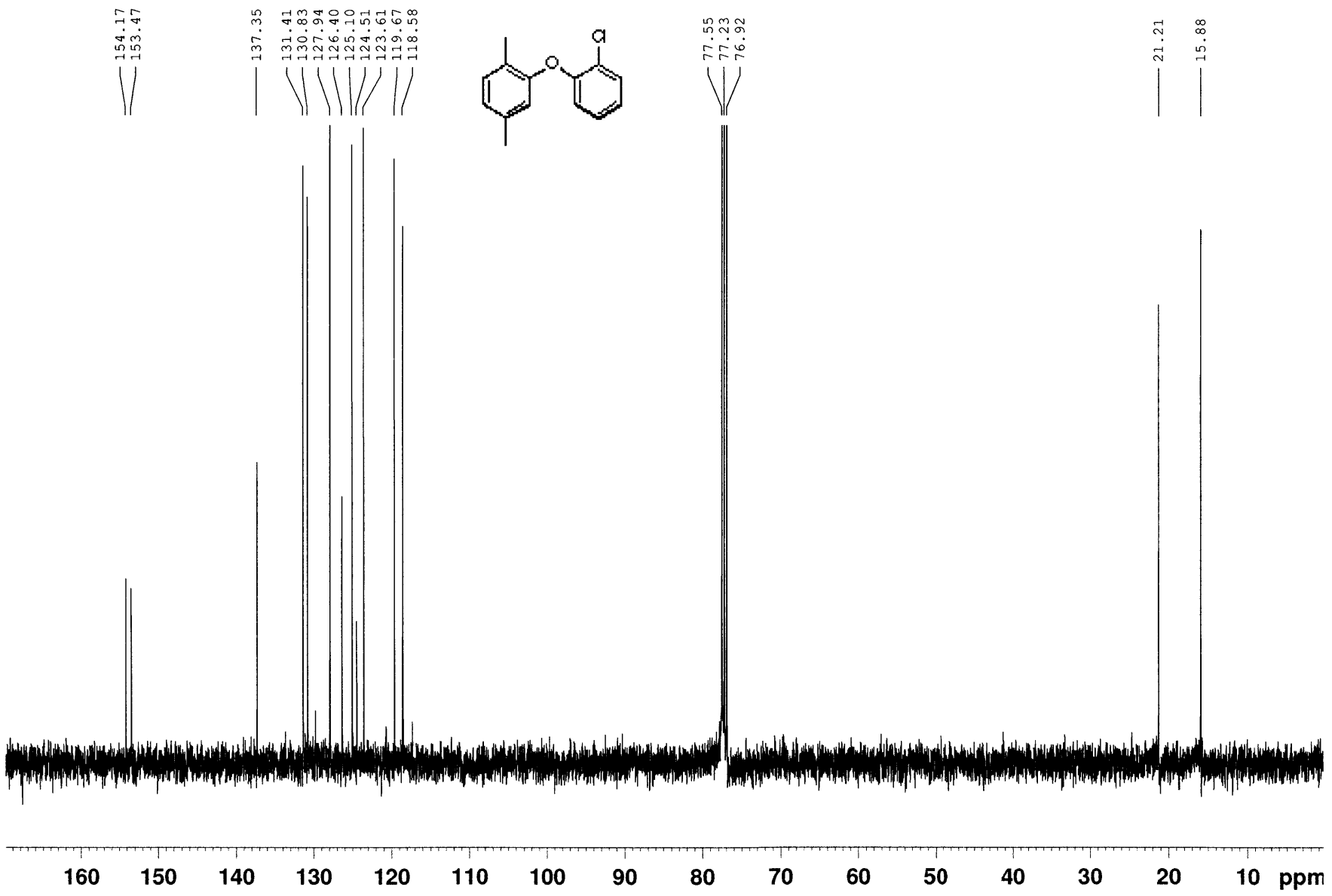
2.18
1.05
1.14
1.04
0.99
3.22
3.49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153.47
137.35
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127.94
126.40
125.10
124.51
123.61
119.67
118.58
77.55
77.23
76.92
21.21
15.88
Cl
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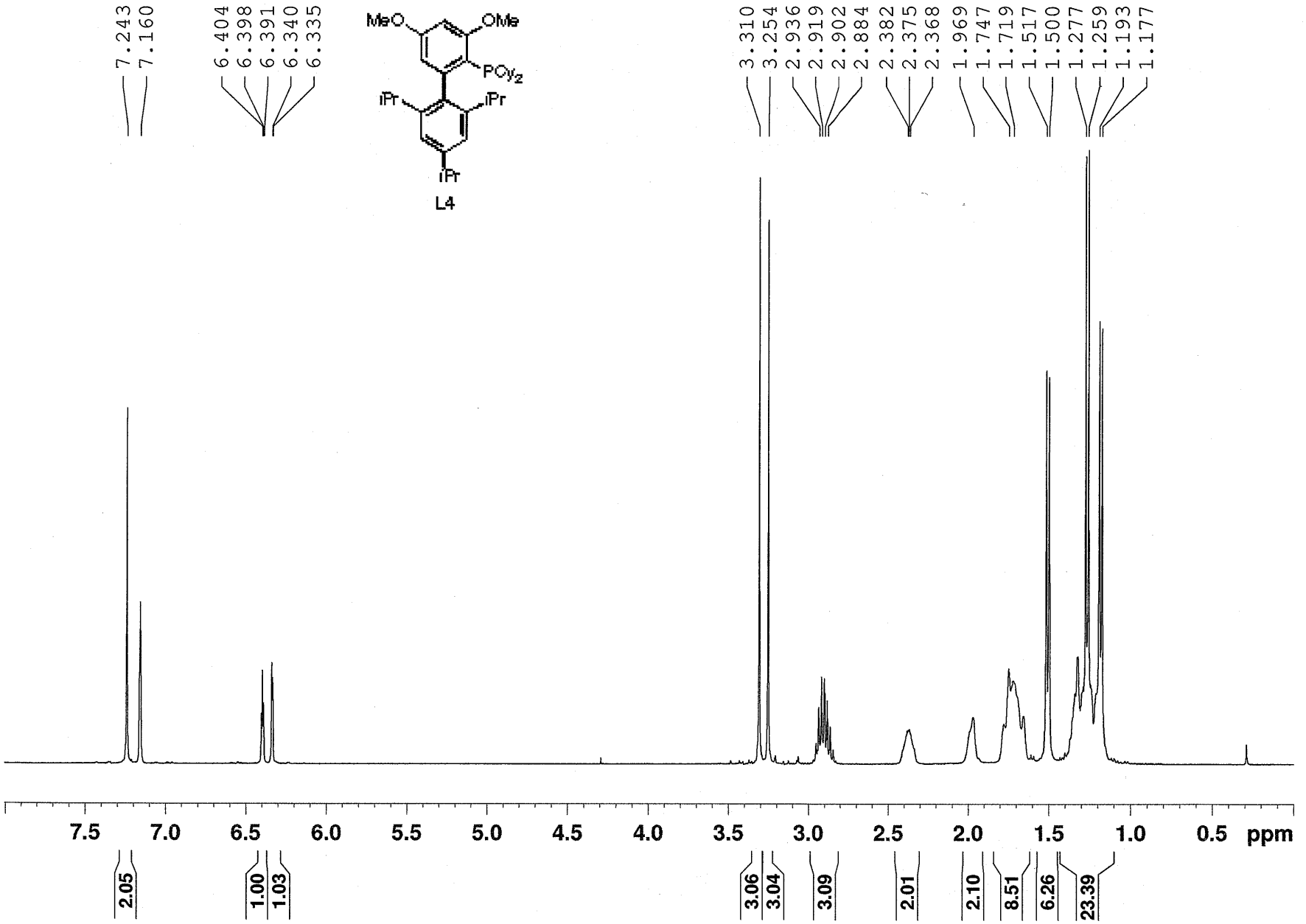
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.160
6.404
6.398
6.391
6.340
6.335
3.310
3.254
2.936
2.919
2.902
2.884
2.382
2.375
2.368
1.969
1.747
1.719
1.517
1.500
1.277
1.259
1.193
1.177
MeO
OMe
POy2
iPr
iPr
iPr
L4
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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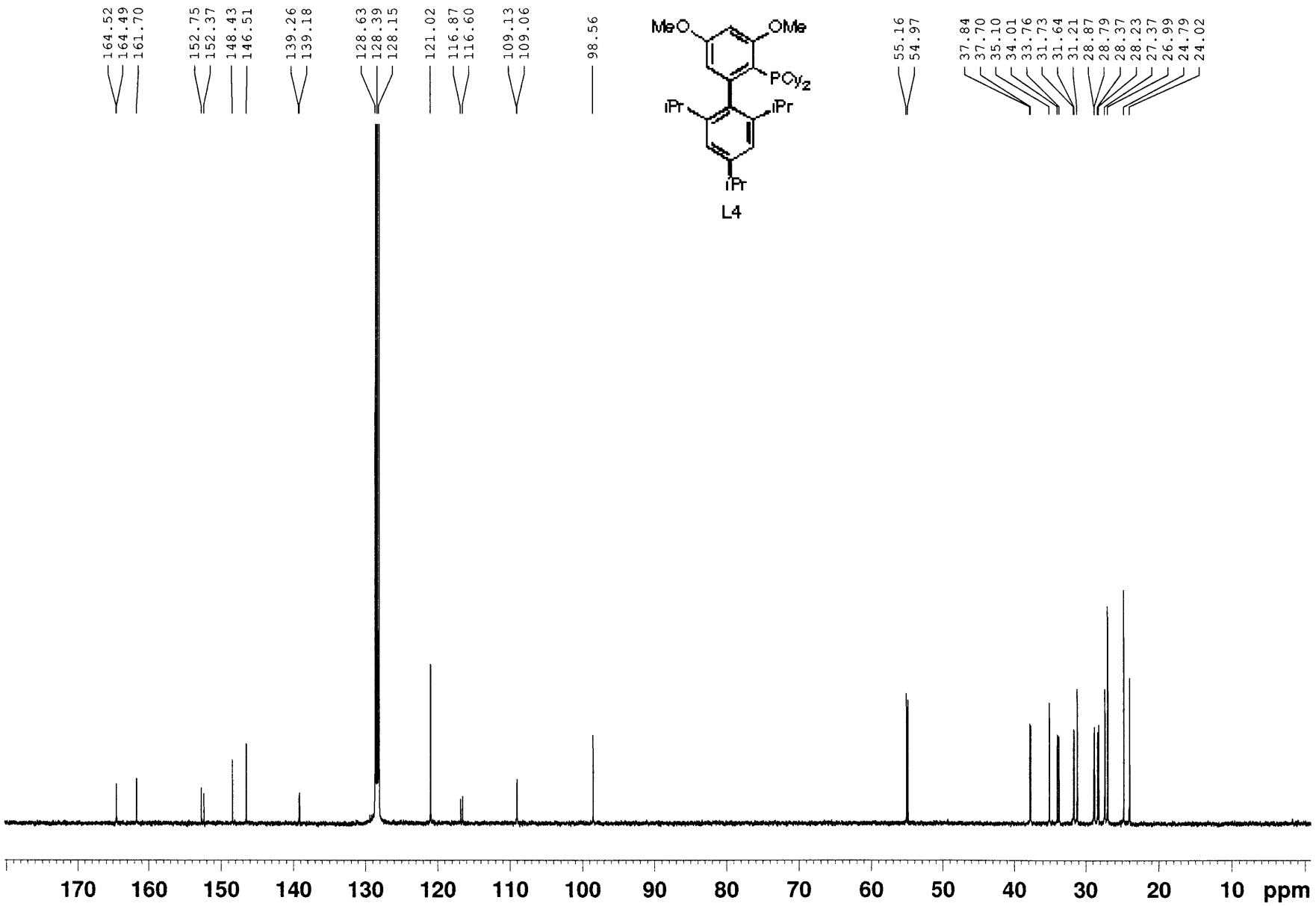
1.00
1.03
3.06
3.04
3.09
2.01
2.10
8.51
6.26
23.39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164.49
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152.75
152.37
148.43
146.51
139.26
139.18
128.63
128.39
128.15
121.02
116.87
116.60
109.13
109.06
98.56
55.16
54.97
37.84
37.70
35.10
34.01
33.76
31.73
31.64
31.21
28.87
28.79
28.37
28.23
27.37
26.99
24.79
24.02
MeO
OMe
PCy2
iPr
iPr
iPr
L4
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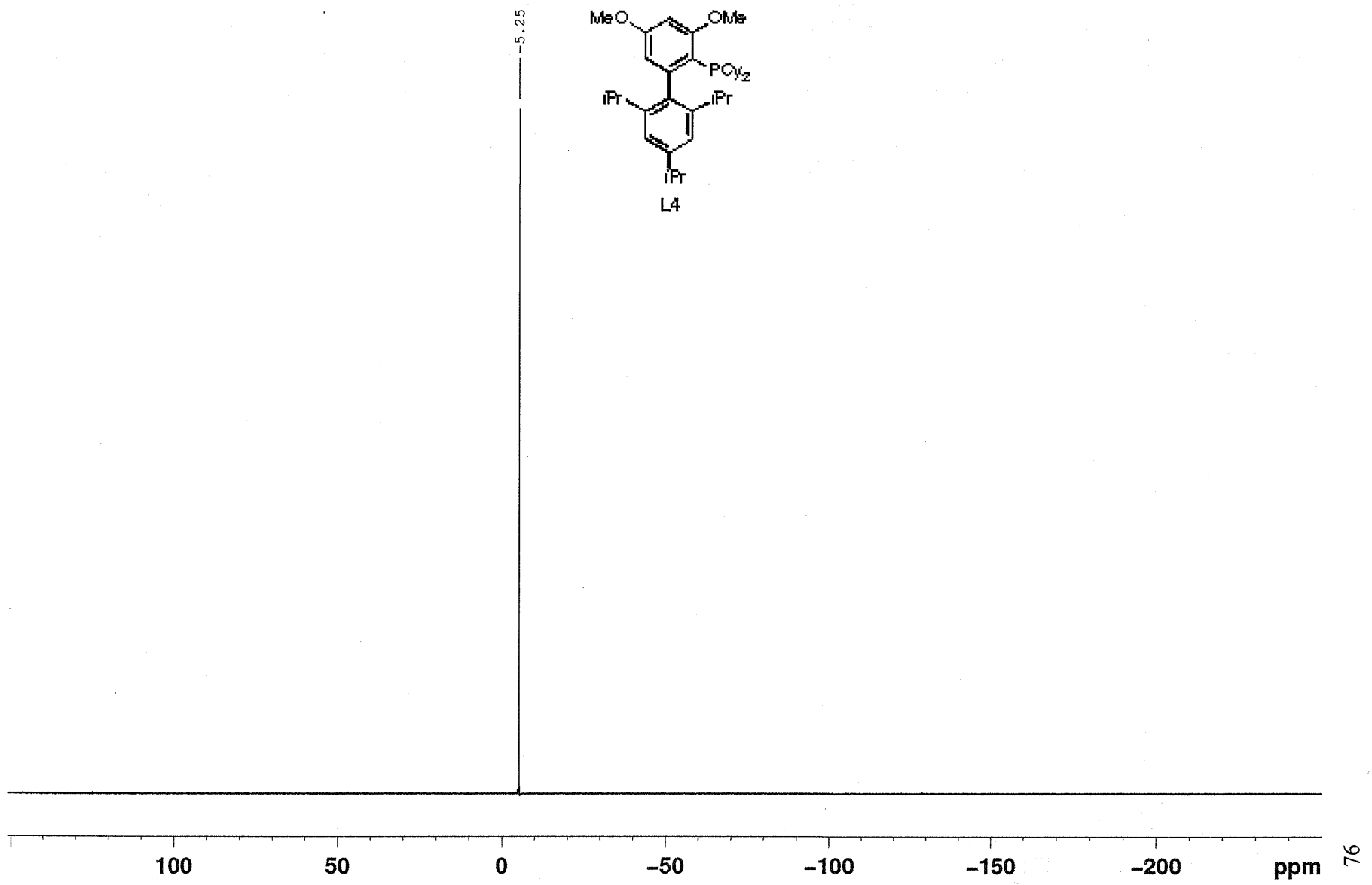
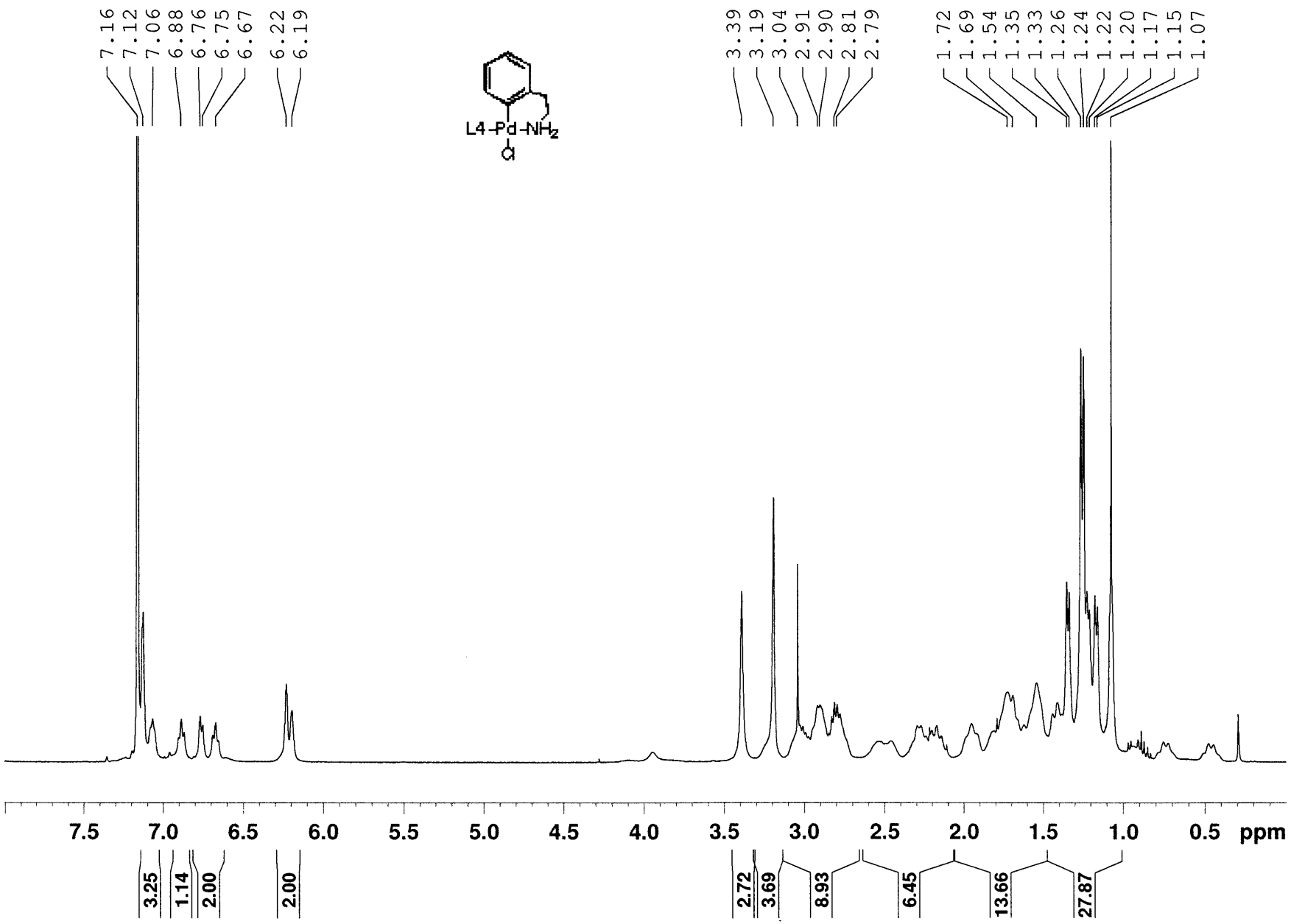
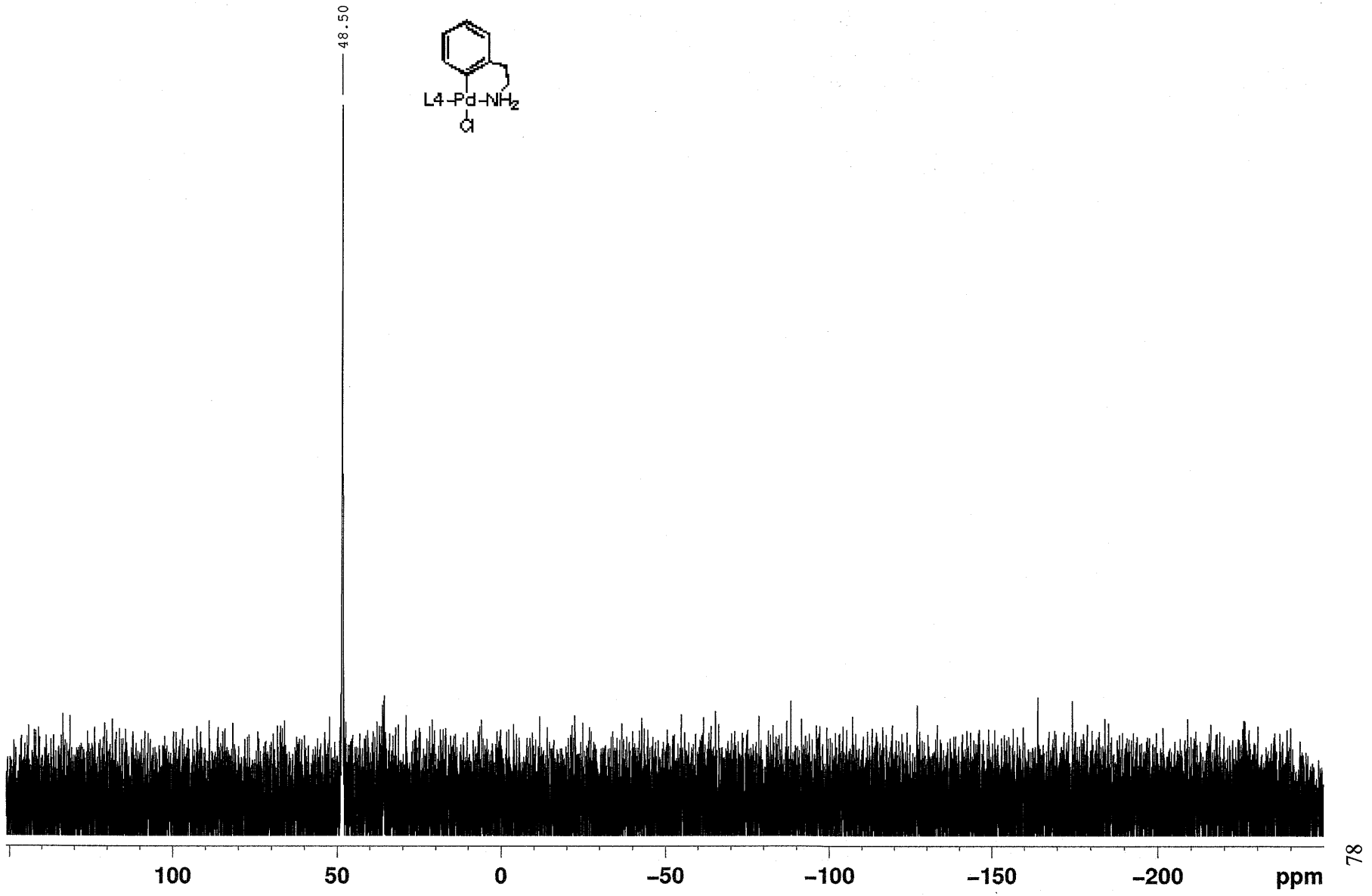
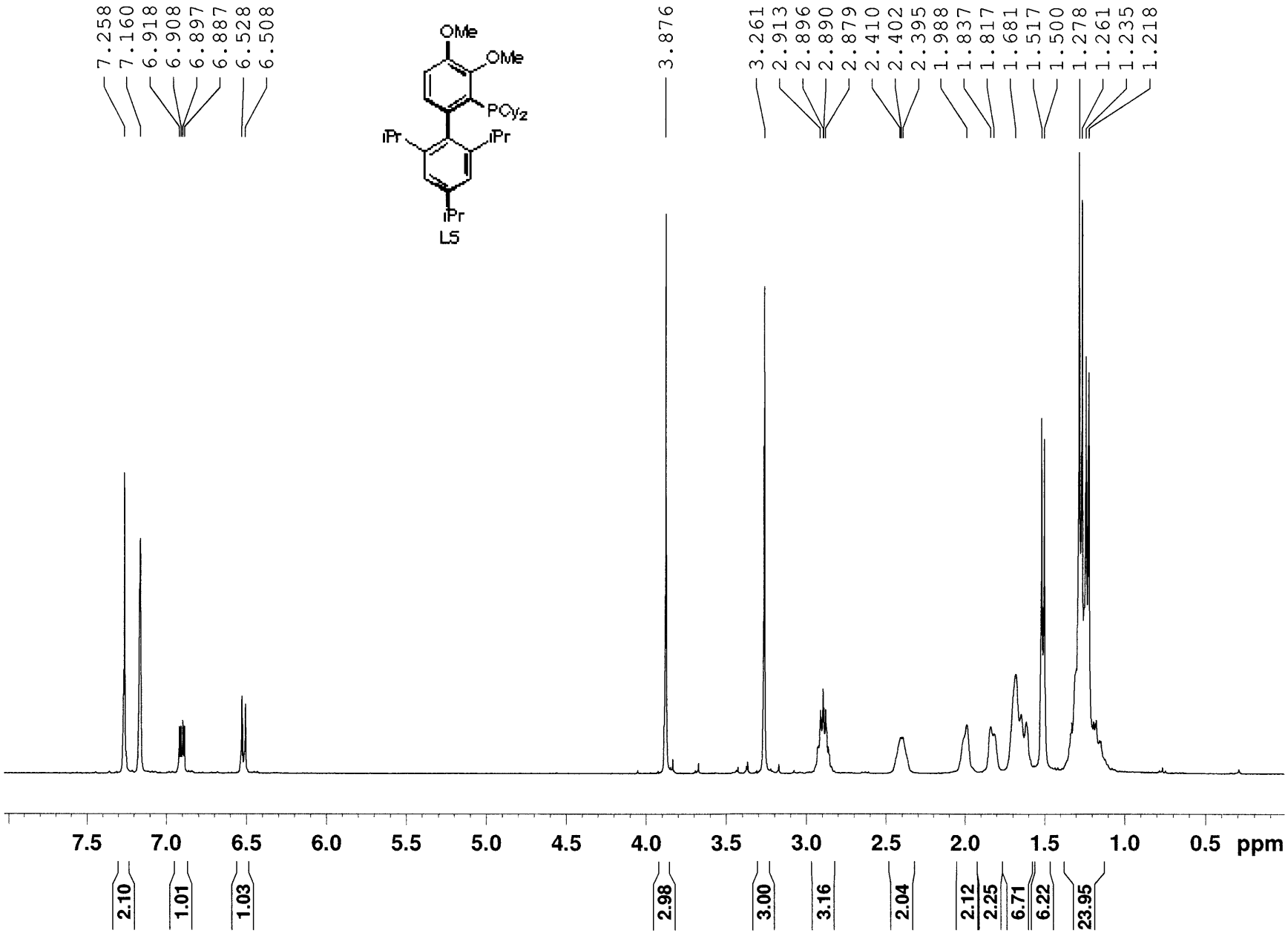
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


5.25
MeO
OMe
PCy2
iPr
iPr
iPr
L4
100
50
0
−50
−100
−150
−200
ppm


7.16
7.12
7.06
6.88
6.76
6.75
6.67
6.22
6.19
3.39
3.19
3.04
2.91
2.90
2.81
2.79
1.72
1.69
1.54
1.35
1.33
1.26
1.24
1.22
1.20
1.17
1.15
1.07
L4-Pd-NH2
Cl
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.25
1.14
2.00
2.00
2.72
3.69
8.93
6.45
13.66
27.87


48.50
L4-Pd-NH2
Cl
100
50
0
-50
-100
-150
-200
ppm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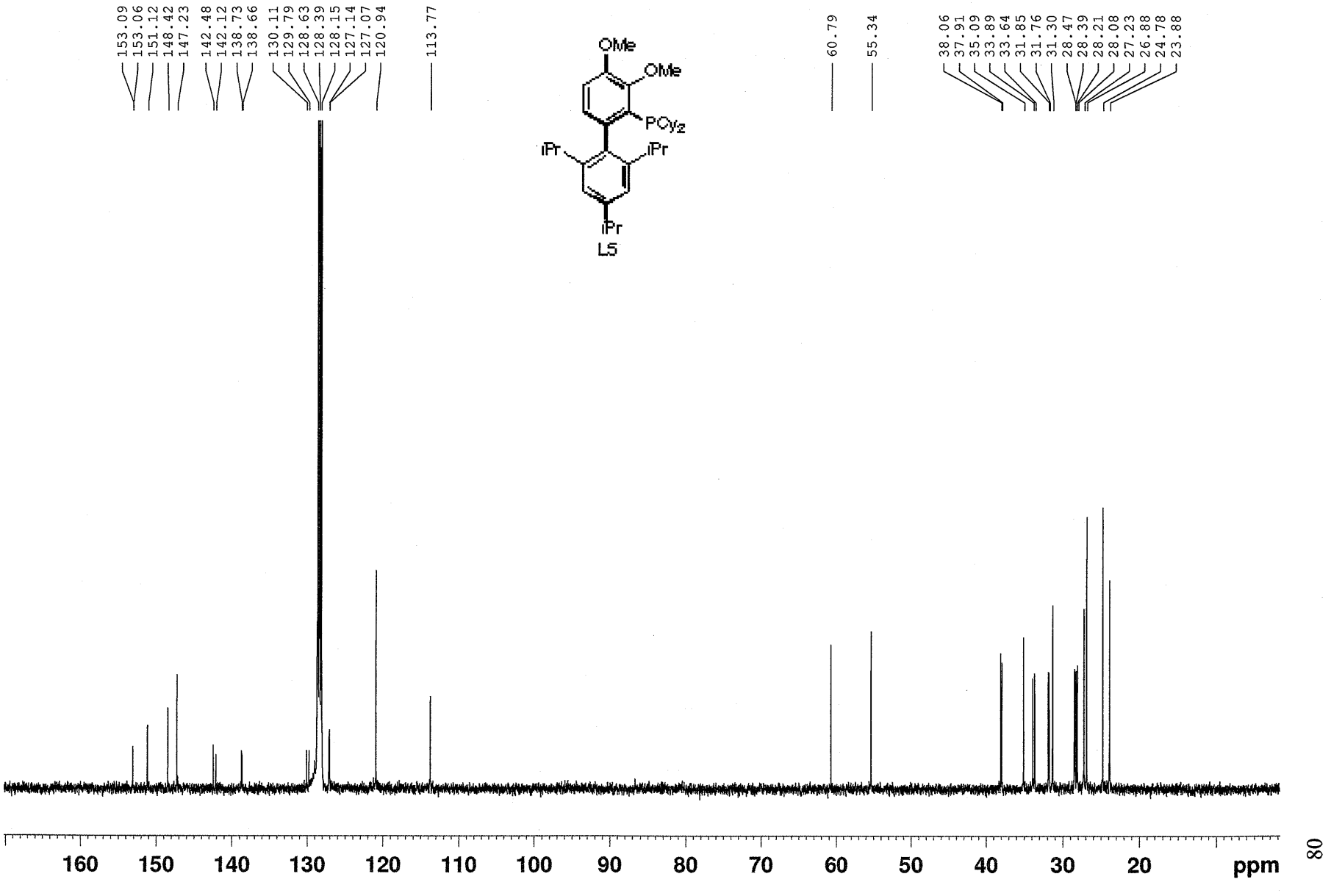
7.160
6.918
6.908
6.897
6.887
6.528
6.508
3.876
3.261
2.913
2.896
2.890
2.879
2.410
2.402
2.395
1.988
1.837
1.817
1.681
1.517
1.500
1.278
1.261
1.235
1.218
OMe
OMe
PCy2
iPr
iPr
iPr
L5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.10
1.01
1.03
2.98
3.00
3.16
2.04
2.12
2.25
6.71
6.22
23.95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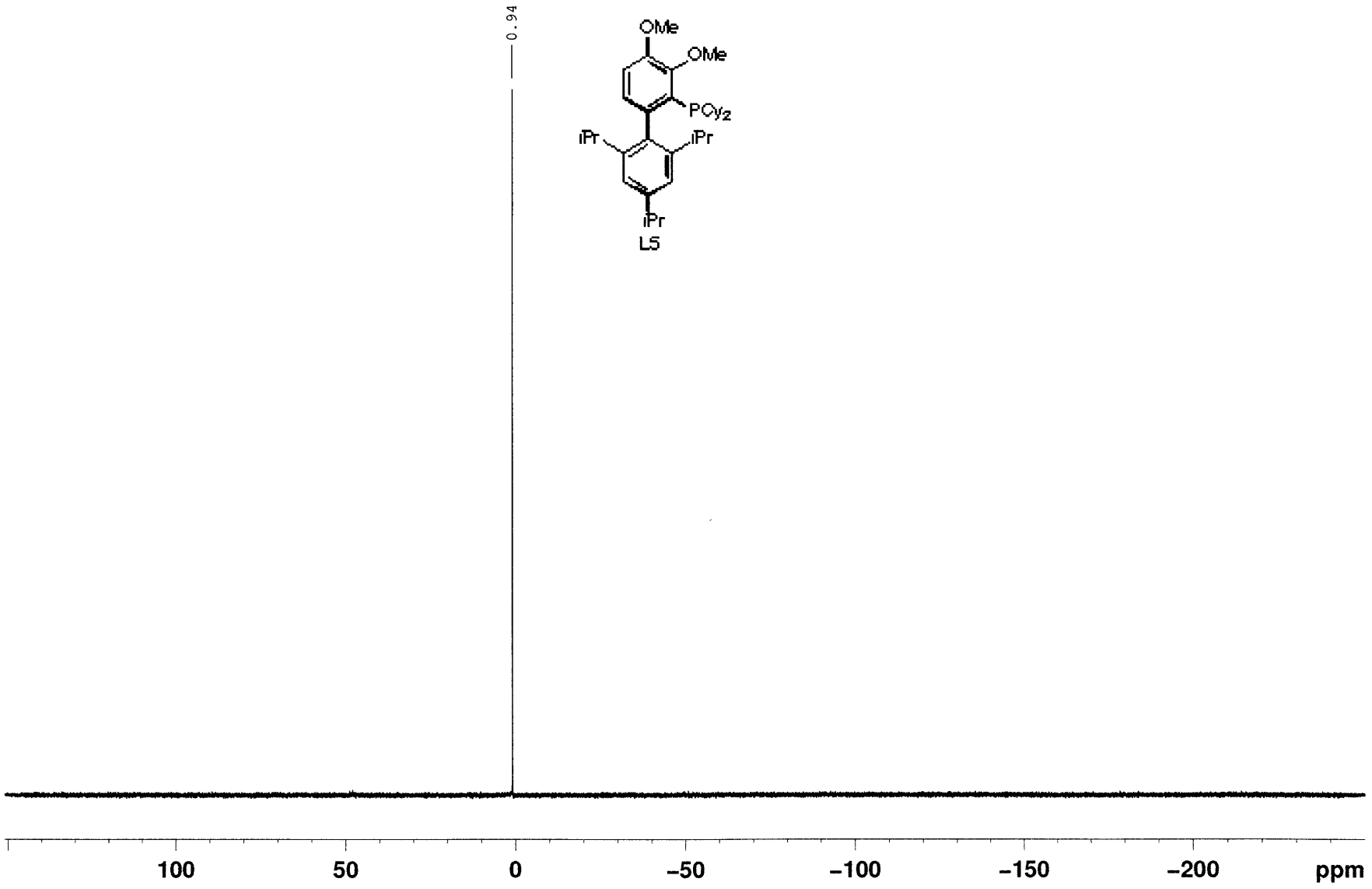
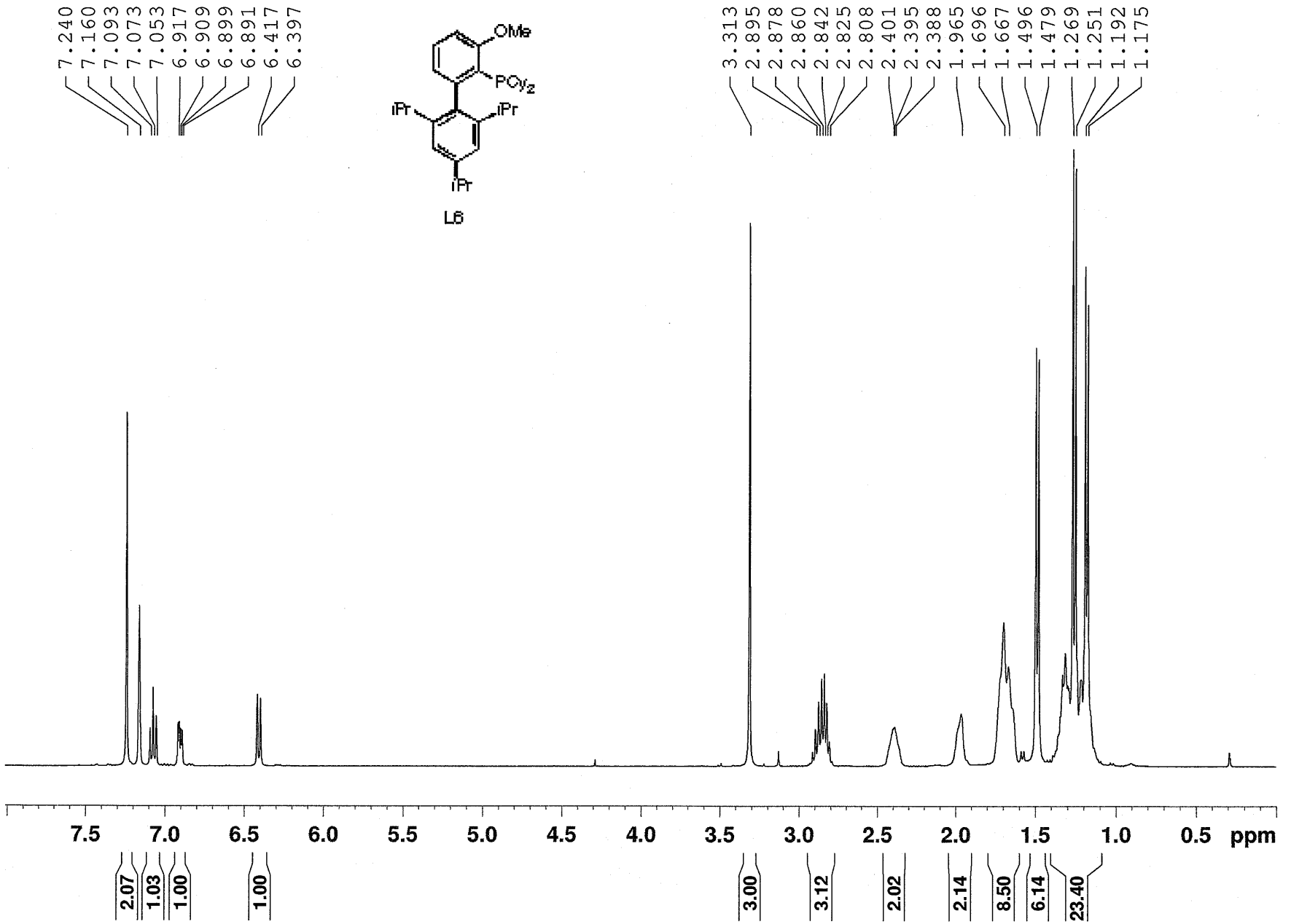
153.06
151.12
148.42
147.23
142.48
142.12
138.73
138.66
130.11
129.79
128.63
128.39
128.15
127.14
127.07
120.94
113.77
60.79
55.34
38.06
37.91
35.09
33.89
33.64
31.85
31.76
31.30
28.47
28.39
28.21
28.08
27.23
26.88
24.78
23.88
OMe
OMe
POy2
iPr
iPr
iPr
L5
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


0.94
OMe
OMe
PCy2
iPr
iPr
iPr
L5
100
50
0
-50
-100
-150
-200
ppm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7.073
7.053
6.917
6.909
6.899
6.891
6.417
6.397
3.313
2.895
2.878
2.860
2.842
2.825
2.808
2.401
2.395
2.388
1.965
1.696
1.667
1.496
1.479
1.269
1.251
1.192
1.175
OMe
PCy2
iPr
iPr
iPr
L6
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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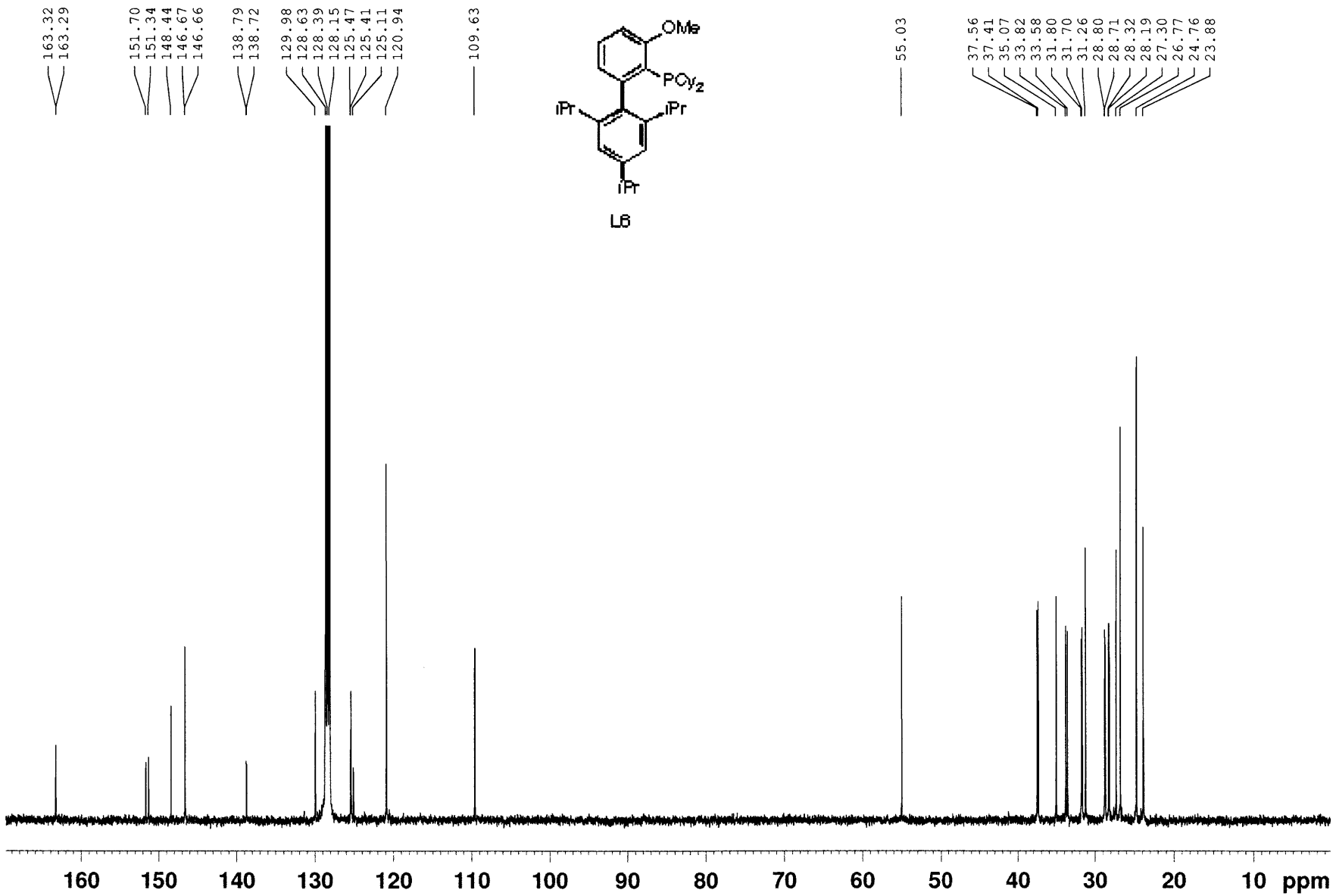
1.03
1.00
1.00
3.00
3.12
2.02
2.14
8.50
6.14
23.40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151.70
151.34
148.44
146.67
146.66
138.79
138.72
129.98
128.63
128.39
128.15
125.47
125.41
125.11
120.94
109.63
55.03
37.56
37.41
35.07
33.82
33.58
31.80
31.70
31.26
28.80
28.71
28.32
28.19
27.30
26.77
24.76
23.88
OMe
POy2
iPr
iPr
iPr
L6
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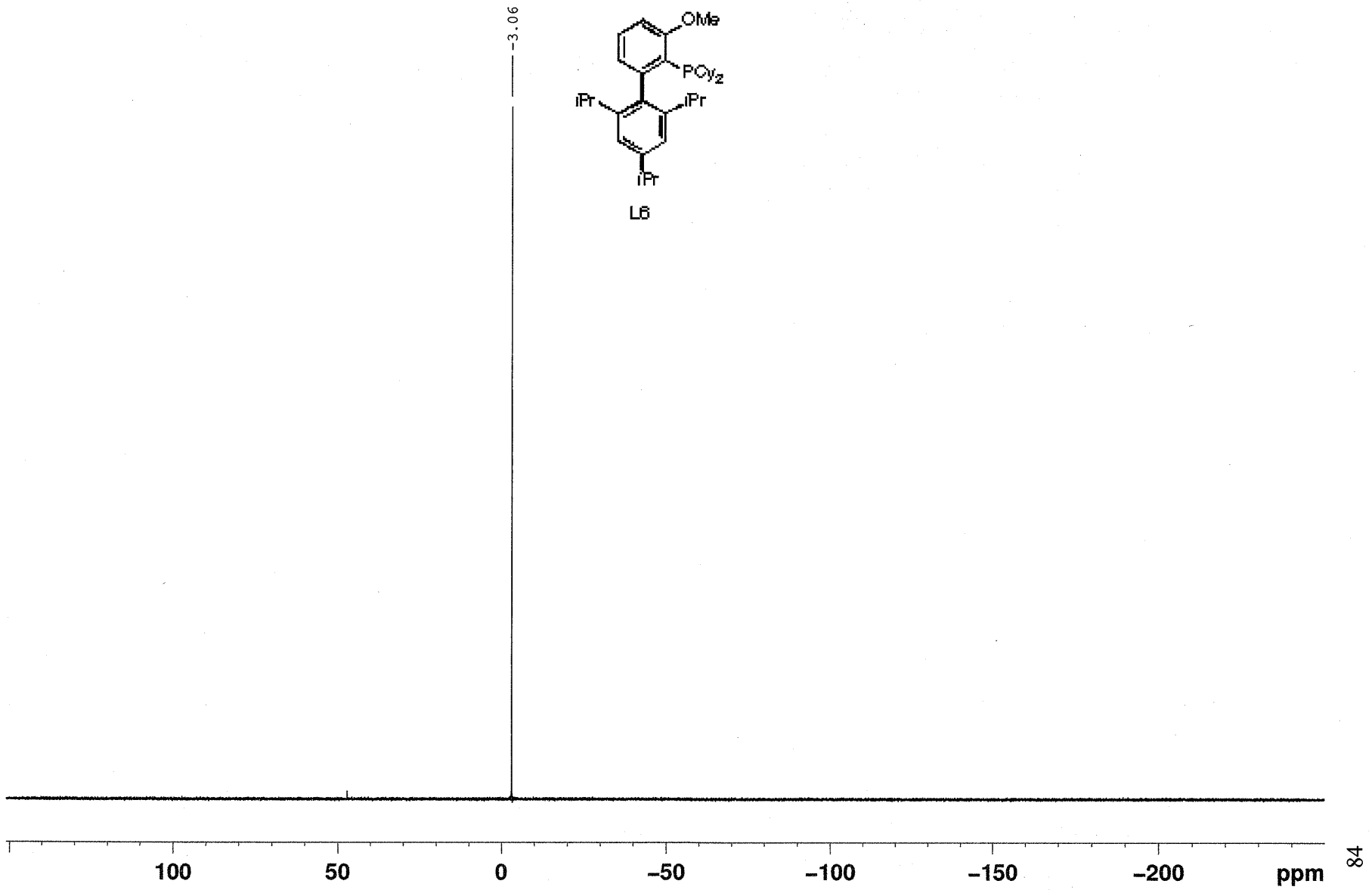
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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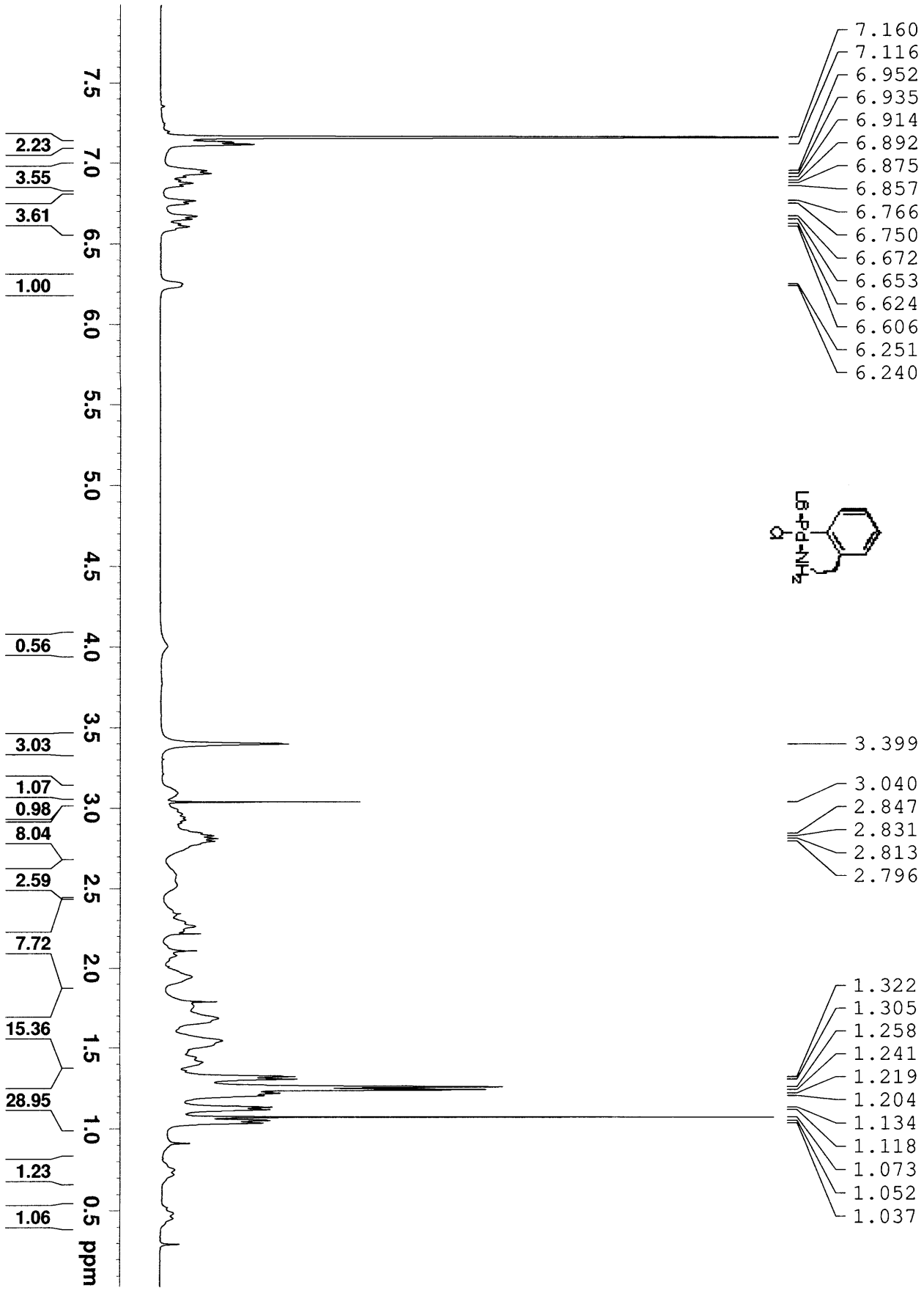
PCy2
iPr
iPr
iPr
L6
100
50
0
-50
-100
-150
-200
ppm


7.160
7.116
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6.892
6.875
6.857
6.766
6.750
6.672
6.653
6.624
6.606
6.251
6.240
3.399
3.040
2.847
2.831
2.813
2.796
1.322
1.305
1.258
1.241
1.219
1.204
1.134
1.118
1.073
1.052
1.037
2.23
3.55
3.61
1.00
0.56
3.03
1.07
0.98
8.04
2.59
7.72
15.36
28.95
1.23
1.06
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
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2.0
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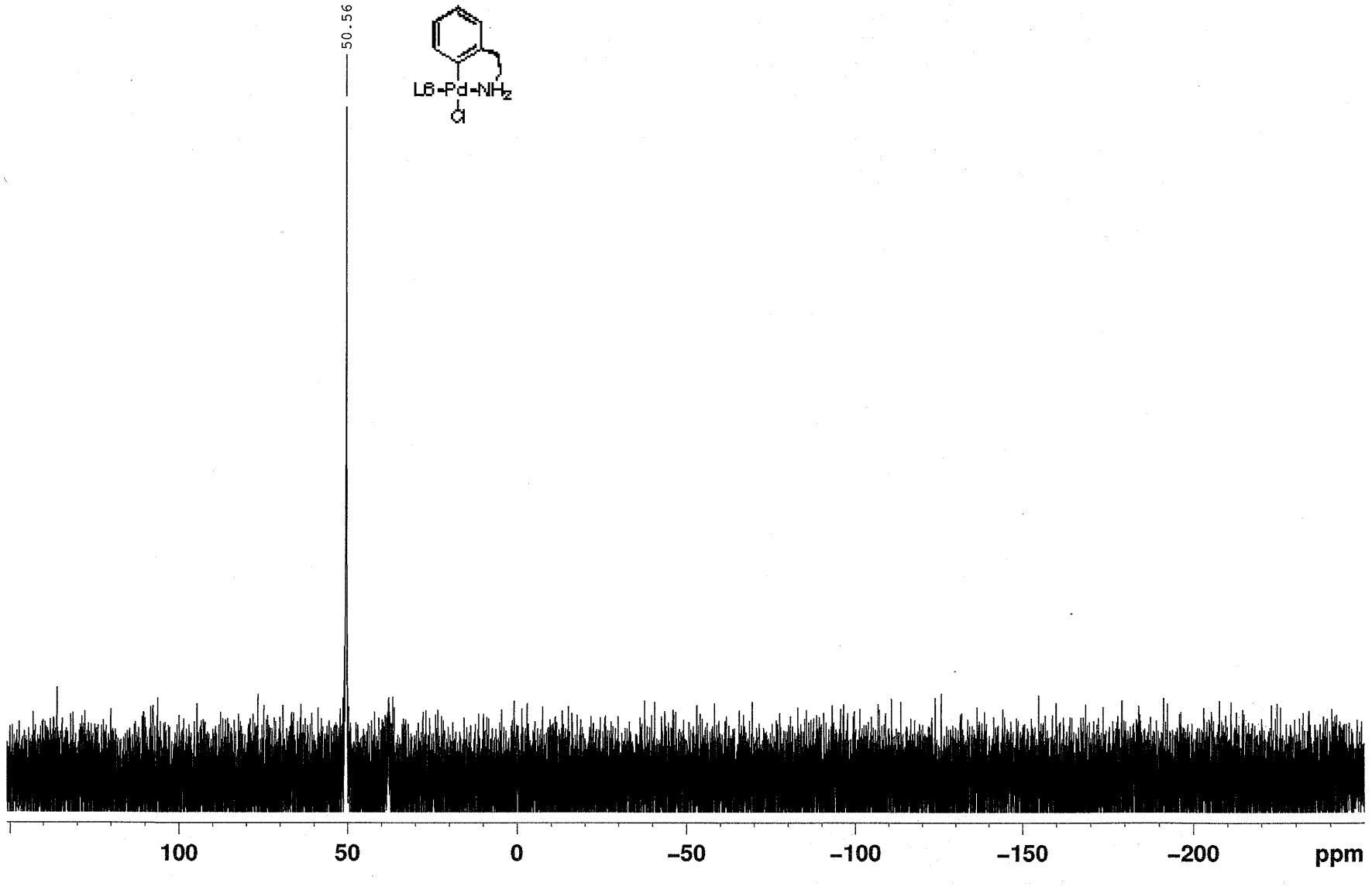
1.0
0.5
ppm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L6-Pd-NH2
Cl
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50
0
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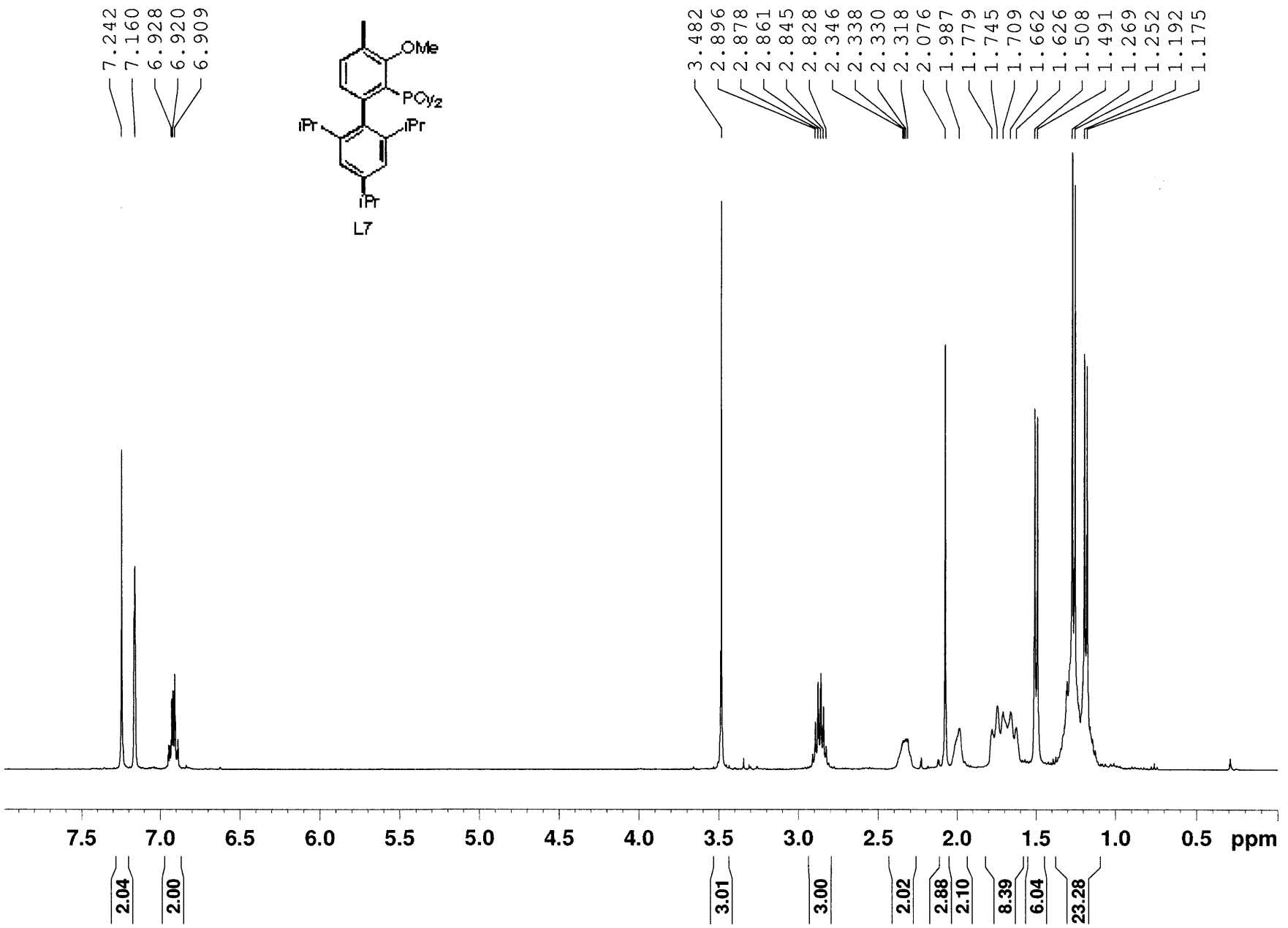
-150
-200
ppm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6.928
6.920
6.909
3.482
2.896
2.878
2.861
2.845
2.828
2.346
2.338
2.330
2.318
2.076
1.987
1.779
1.745
1.709
1.662
1.626
1.508
1.491
1.269
1.252
1.192
1.175
OMe
PCy2
iPr
iPr
iPr
L7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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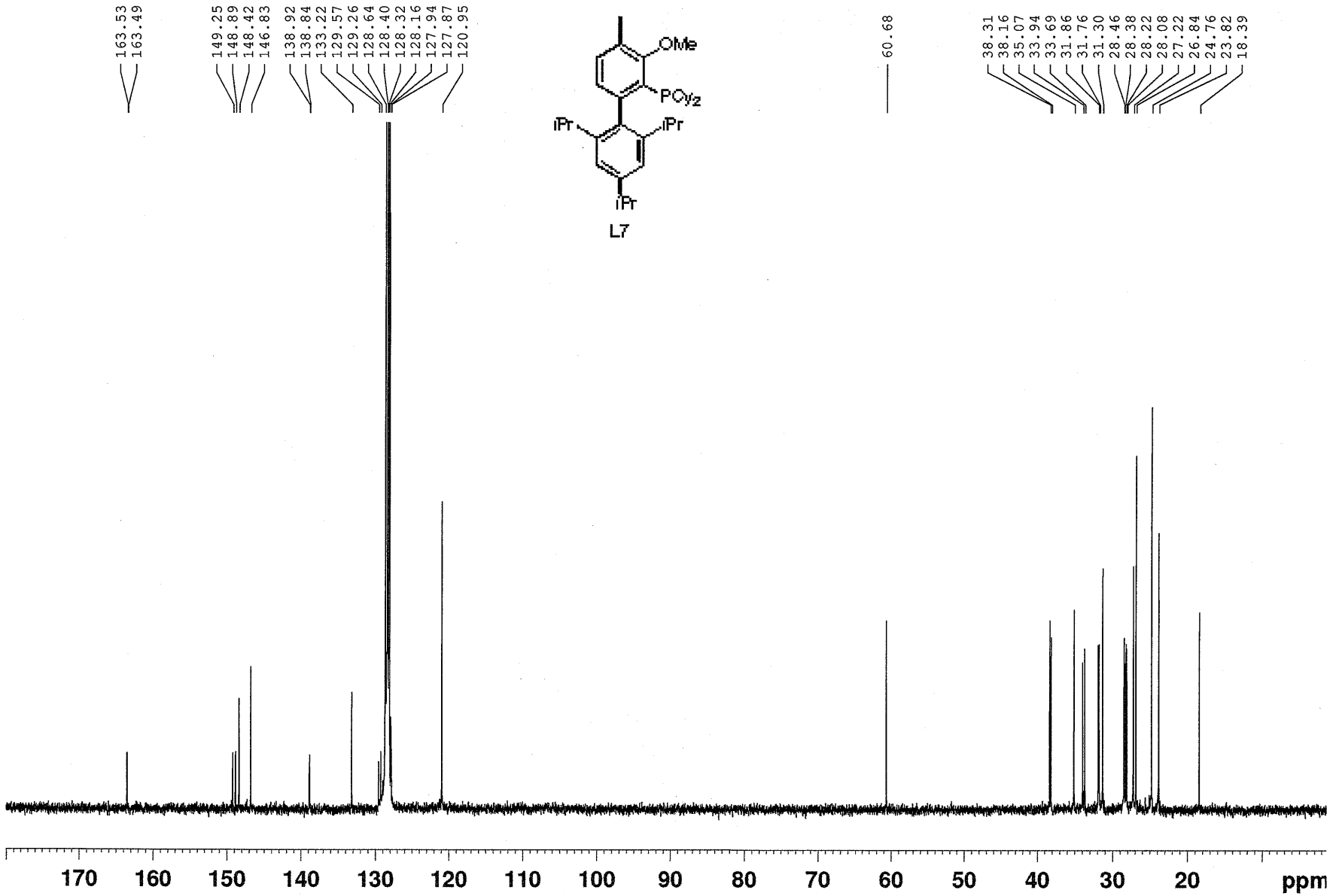
2.00
3.01
3.00
2.02
2.88
2.10
8.39
6.04
23.28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148.89
148.42
146.83
138.92
138.84
133.22
129.57
129.26
128.64
128.40
128.32
128.16
127.94
127.87
120.95
60.68
38.31
38.16
35.07
33.94
33.69
31.86
31.76
31.30
28.46
28.38
28.22
28.08
27.22
26.84
24.76
23.82
18.39
OMe
POy2
iPr
iPr
iPr
L7
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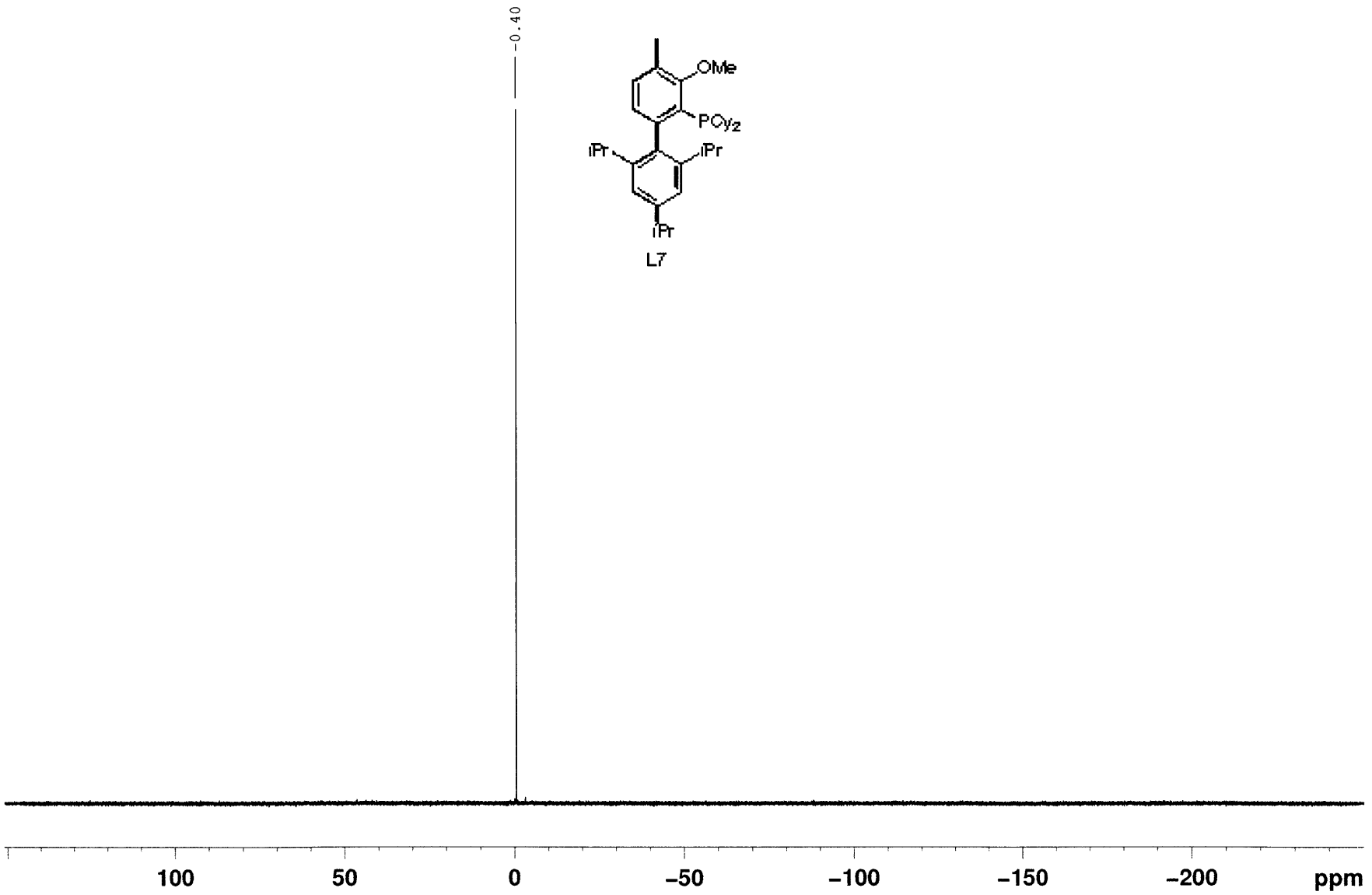
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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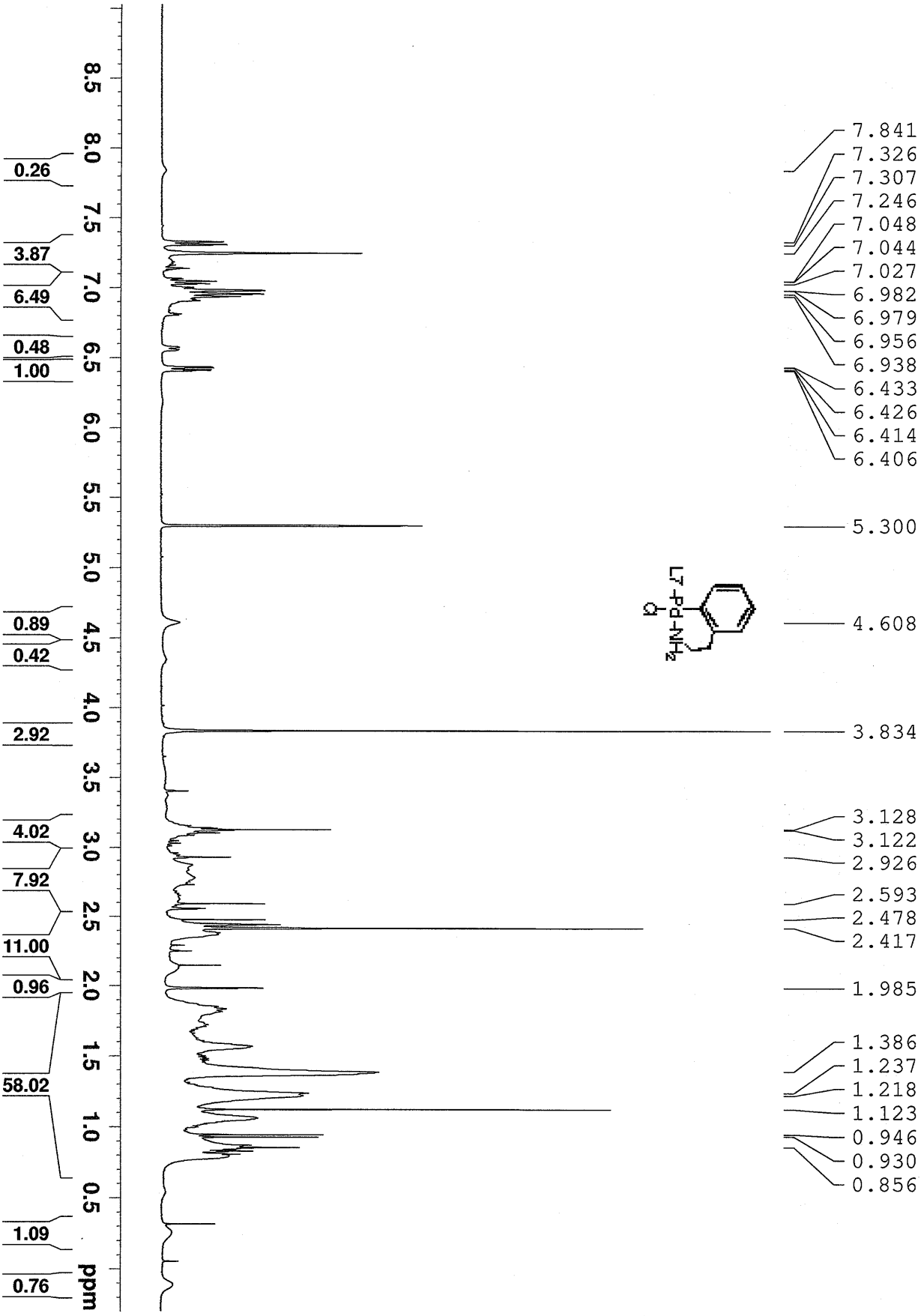
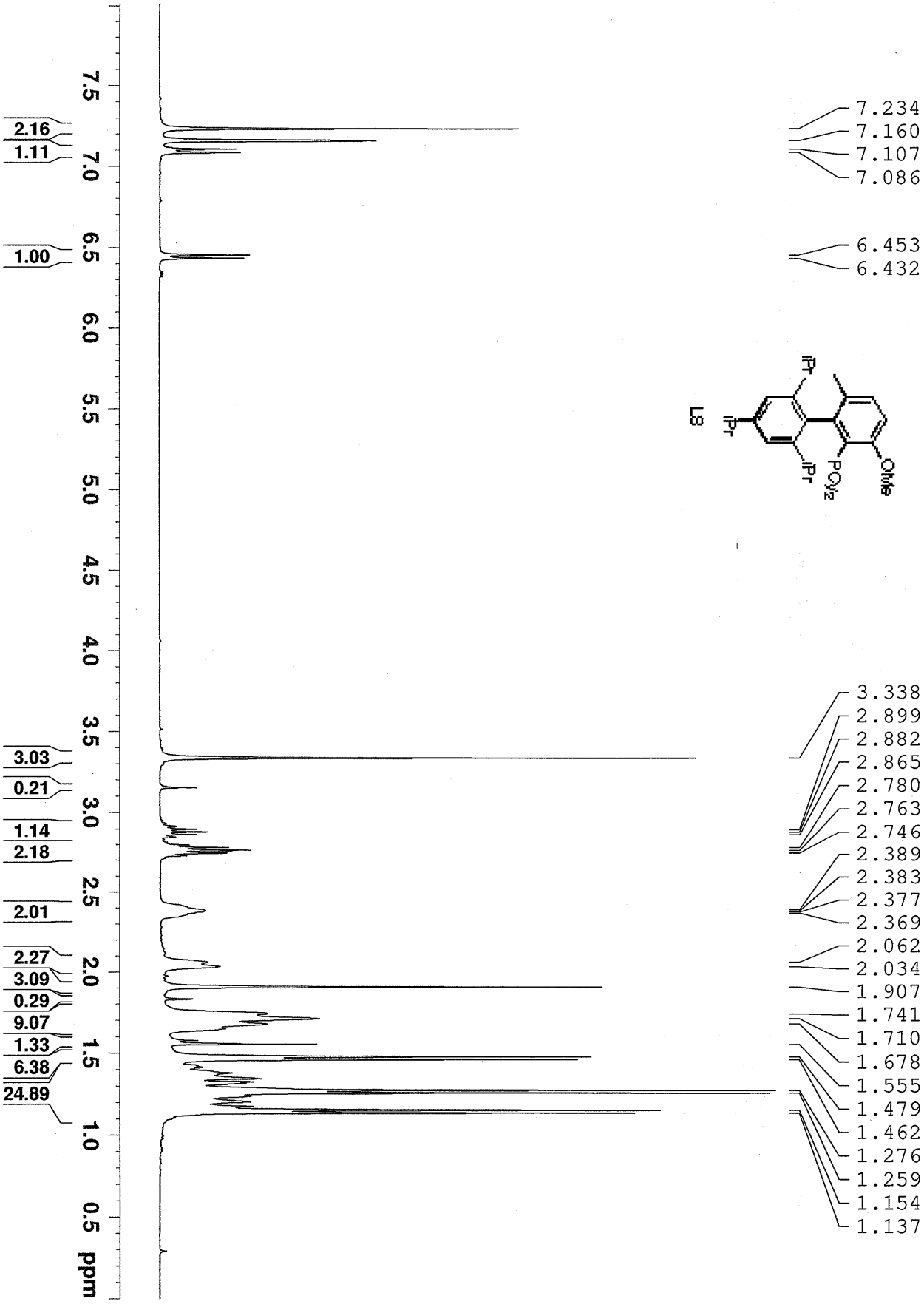
PCy2
iPr
iPr
iPr
L7
100
50
0
−50
−100
−150
−200
ppm


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.26
3.87
6.49
0.48
1.00
0.89
0.42
2.92
4.02
7.92
11.00
0.96
58.02
1.09
0.76
L7-Pd-NH2
Cl
7.841
7.326
7.307
7.246
7.048
7.044
7.027
6.982
6.979
6.956
6.938
6.433
6.426
6.414
6.406
5.300
4.608
3.834
3.128
3.122
2.926
2.593
2.478
2.417
1.985
1.386
1.237
1.218
1.123
0.946
0.930
0.856

42.88
L7-Pd-NH2
Cl
100
50
0
-50
-100
-150
-200
ppm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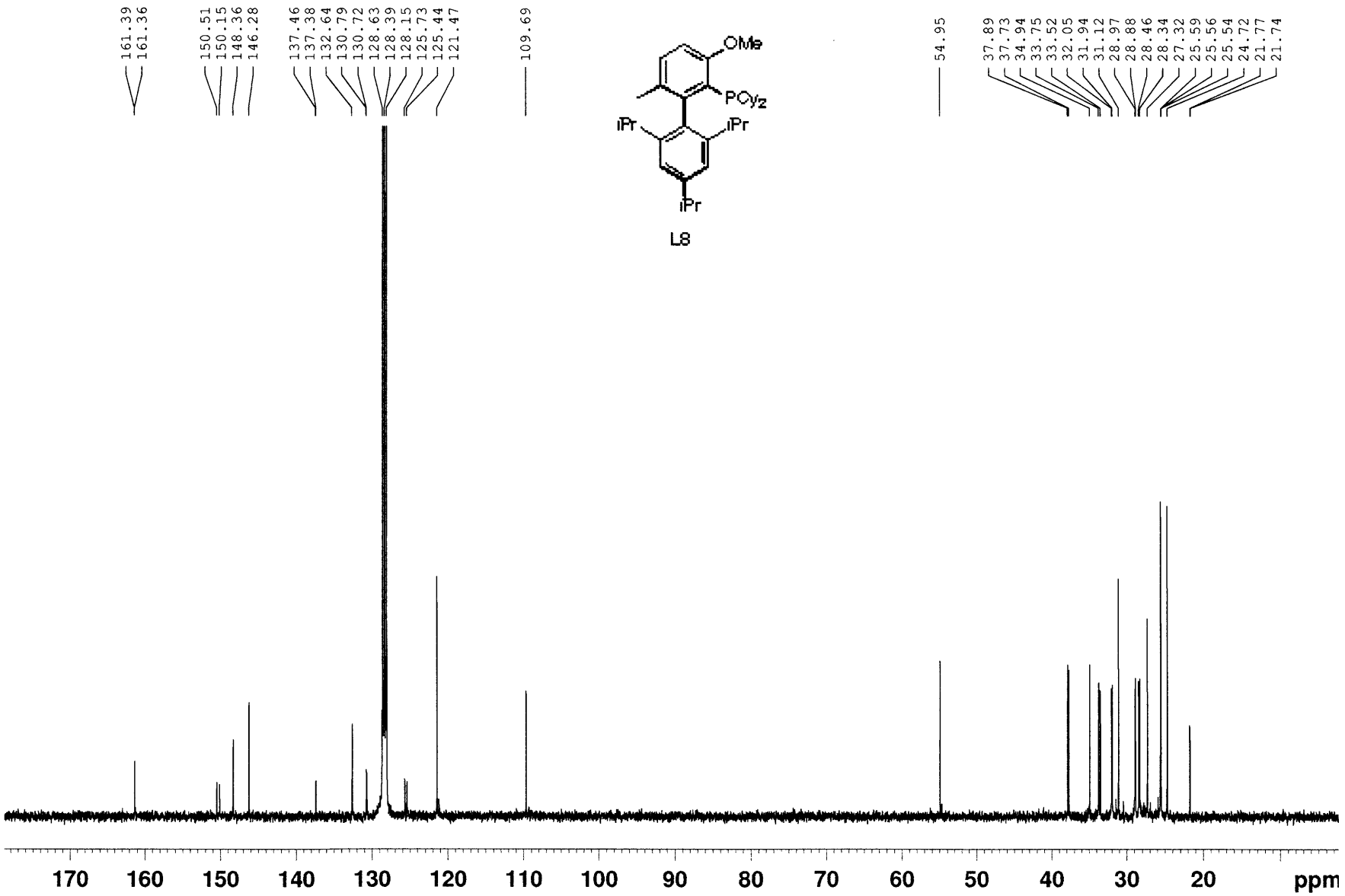
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.16
1.11
1.00
3.03
0.21
1.14
2.18
2.01
2.27
3.09
0.29
9.07
1.33
6.38
24.89
7.234
7.160
7.107
7.086
6.453
6.432
3.338
2.899
2.882
2.865
2.780
2.763
2.746
2.389
2.383
2.377
2.369
2.062
2.034
1.907
1.741
1.710
1.678
1.555
1.479
1.462
1.276
1.259
1.154
1.137
L8
iPr
iPr
iPr
PCy2
OMe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150.51
150.15
148.36
146.28
137.46
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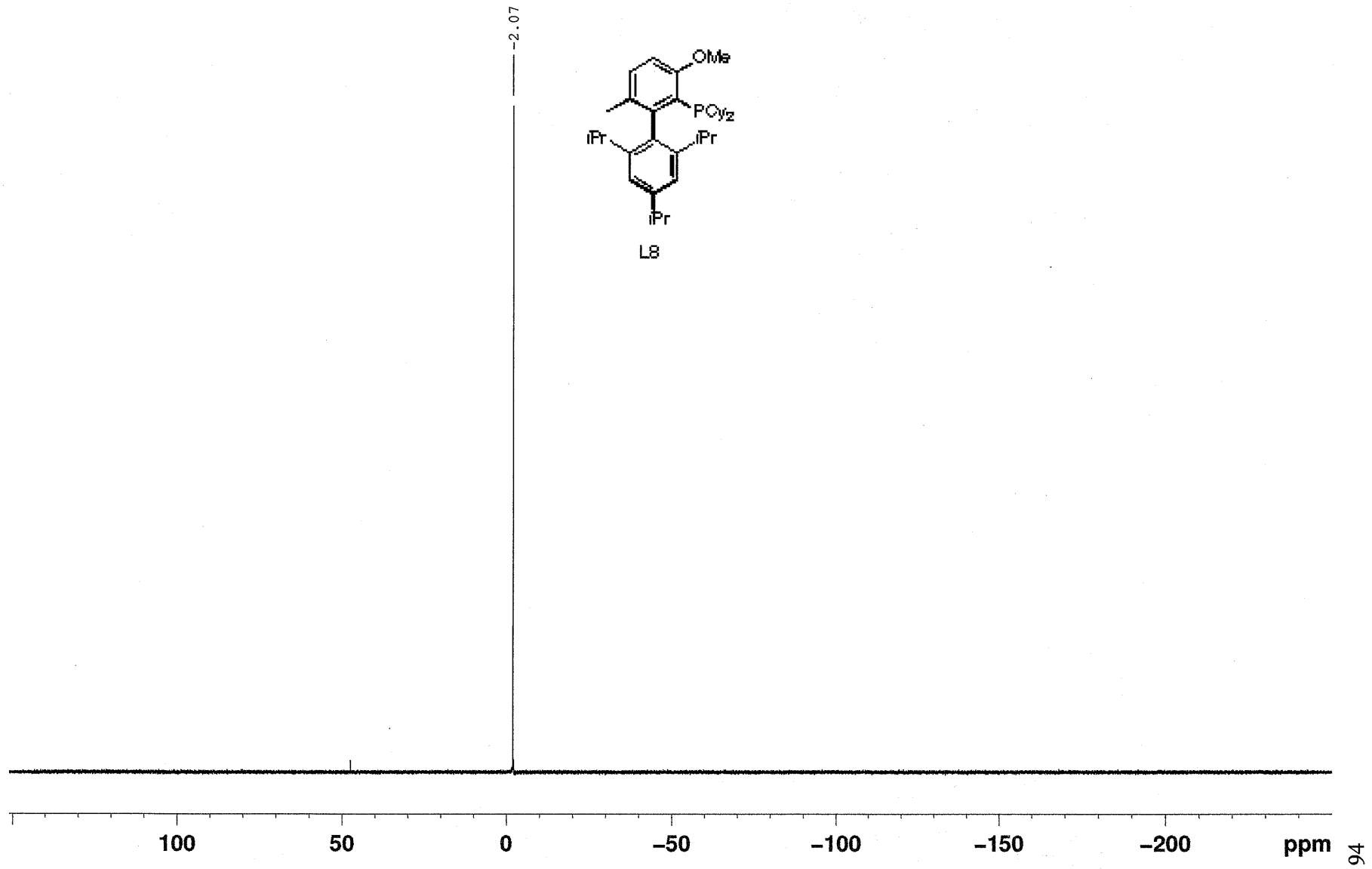
130.79
130.72
128.63
128.39
128.15
125.73
125.44
121.47
109.69
54.95
37.89
37.73
34.94
33.75
33.52
32.05
31.94
31.12
28.97
28.88
28.46
28.34
27.32
25.59
25.56
25.54
24.72
21.77
21.74
OMe
PCy2
iPr
iPr
iPr
L8
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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OMe
PCy2
iPr
iPr
iPr
L8
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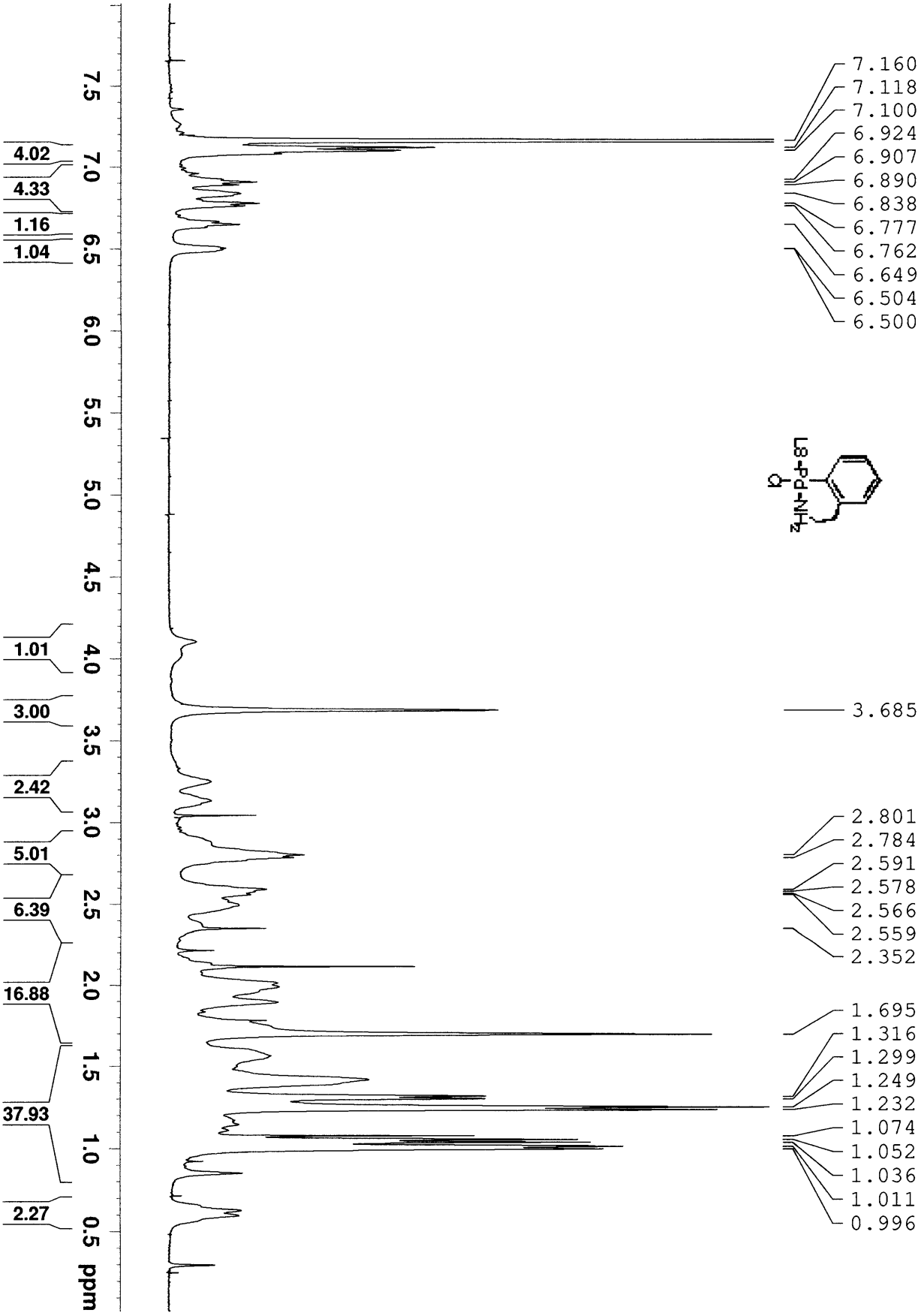
50
0
-50
-100
-150
-200
ppm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7.118
7.100
6.924
6.907
6.890
6.838
6.777
6.762
6.649
6.504
6.500
3.685
2.801
2.784
2.591
2.578
2.566
2.559
2.352
1.695
1.316
1.299
1.249
1.232
1.074
1.052
1.036
1.011
0.996
4.02
4.33
1.16
1.04
1.01
3.00
2.42
5.01
6.39
16.88
37.93
2.27
7.5
7.0
6.5
6.0
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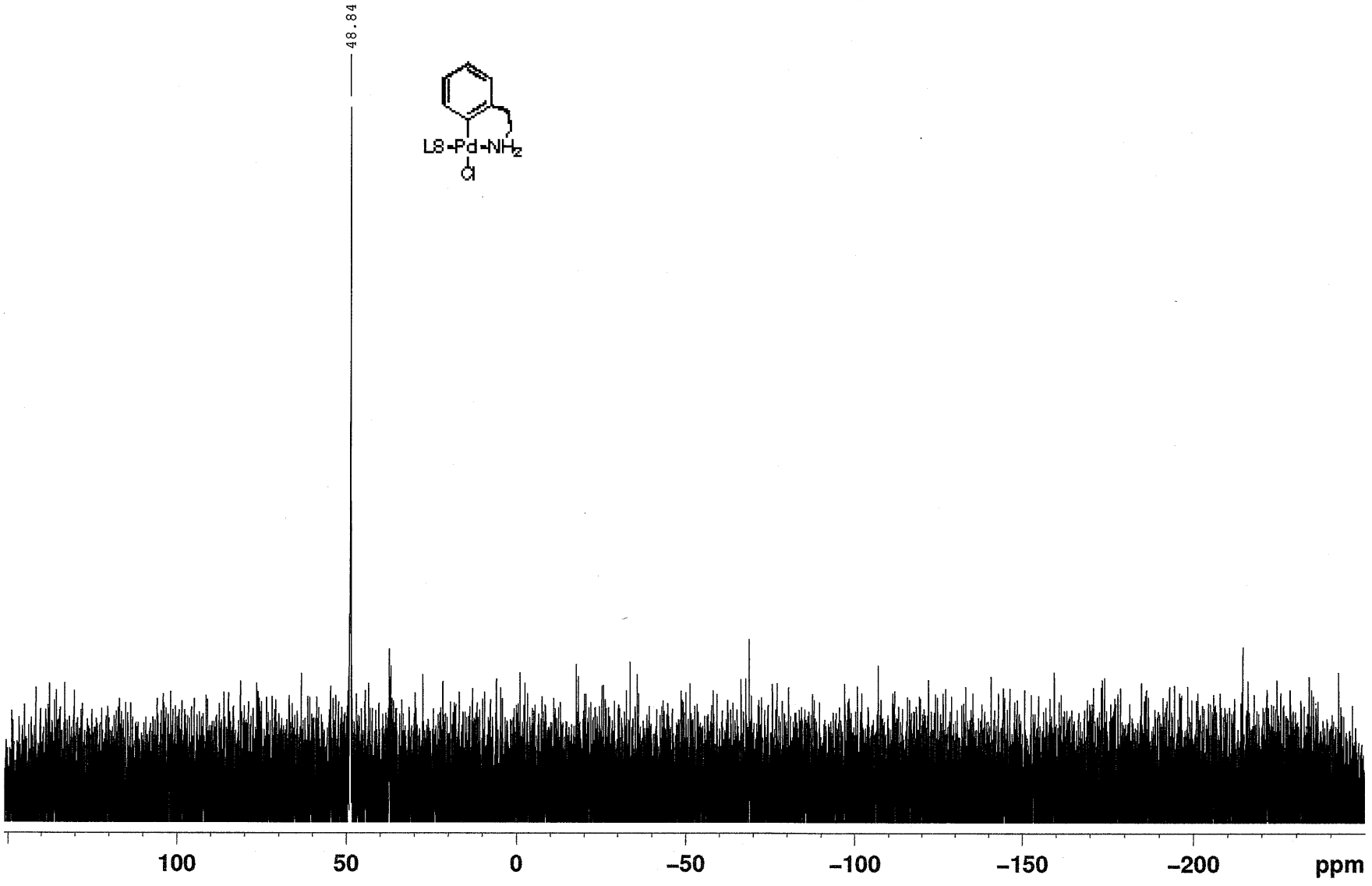
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


48.84
LS-Pd-NH2
Cl
100
50
0
-50
-100
-150
-200
ppm

Appendix B. Curriculum Vitae

Nicole R. Davis

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Cambridge, MA 02139 E-mail: davis.nr@gmail.com

Education

Massachusetts Institute of Technology
Science Masters in Organic Chemistry, expected July 2009

University of California, Berkeley
Bachelors of Science with High Honors in Chemistry, May 2005
Honors: Saegebarth Prize in Chemistry, Phi Beta Kappa

Research Experience

Research Assistant with Professor Stephen L. Buchwald
Massachusetts Institute of Technology, Cambridge, MA (01/08-06/09)
Masters Thesis: Synthesis and Study of Ligands for Palladium-Catalyzed C-O and C-N Coupling

Scientific Associate I
Novartis Institutes for Biomedical Research, Cambridge, MA (10/05-06/07)
Organic chemist in Oncology Department

- Developed reliable, scalable synthetic route to class of molecules, used for > 20 analogs
- Prepared large scale batches of five compounds requiring seven-step routes for *in vivo* studies
- Developed routes to, synthesized, and purified dozens of potential drugs for biological evaluation

Research Assistant with Professor F. Dean Toste
College of Chemistry, U.C. Berkeley, Berkeley, CA (9/04-8/05)
Research Topic: Gold(I)-catalyzed pyrrole synthesis: cyclization of homopropargyl azides

- Synthesized several substrates via multi-step routes
- Completed mechanistic study utilizing deuterium labeled substrate

Research Assistant with Professor Andrew Streitwieser
College of Chemistry, U.C. Berkeley, Berkeley, CA (5/04-8/04)
Research Topic: Modeling transition states and kinetic isotope effects of lithium amide deprotonations of arenes. Modeling phosphine basicities in solution.

- Performed *ab initio* calculations on ground state and transition state structures using Gaussian
- Compiled literature data for comparison with calculations

Publications

Fors, B. P.; Davis, N. R.; Buchwald, S. L. "An Efficient Process for Pd-Catalyzed C-N Cross-Coupling Reactions of Aryl Iodides: Insight into Controlling Factors." *J. Am. Chem. Soc.* **2009**, *131*, 5766-5768.

Gorin, D. J.; Davis, N. R.; Toste, F. D. "Gold(I)-Catalyzed Intramolecular Acetylenic Schmidt Reaction." *J. Am. Chem. Soc.* **2005**, *127*, 11260-11261.

Streitwieser, A.; McKeown, A. E.; Hasanayn, F.; Davis, N. R. "Basicity of Some Phosphines in THF." *Org. Lett.* **2005**, *7*, 1259-1262.

Teaching Experience

Teaching Assistant for Organic Chemistry I
Massachusetts Institute of Technology, Cambridge, MA (09/07-06/08)
Head TA/ recitation instructor
Received outstanding teaching award